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Neural Correlates of Physical Abuse in Childhood

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Neural Correlates of Physical Abuse in Childhood

Lena Lim

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the degree of
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Abstract

Childhood maltreatment is associated with impaired inhibition, attention, emotion processing and hypersensitivity to mistakes. This thesis includes a meta-analysis of published whole-brain voxel-based morphometry studies in childhood maltreatment to elucidate the most robust volumetric grey matter (GM) abnormalities and an fMRI study that examined the association between childhood (physical) abuse and brain functionality in the domains of inhibition, attention, error and emotion processing. The participants were medication naïve, drug-free young people and psychiatric comorbidities were controlled for by including a psychiatric control group.

Anisotropic effect size-signed differential mapping was used to conduct the meta-analysis. For the fMRI study, brain activation was compared between 23 age- and gender-matched young people who had experienced childhood (physical) abuse, 20 psychiatric controls matched for psychiatric diagnoses with the participants exposed to abuse and 27 healthy controls while they performed a tracking stop-signal task designed to elicit 50% inhibition failures, a parametrically modulated vigilance task and an emotion processing task.

The meta-analysis showed that the most consistent GM abnormalities in childhood maltreatment were in relatively late-developing ventrolateral prefrontal- limbic-temporal regions. The participants who had experienced abuse showed hyperactivation in typical error processing regions of the dorsomedial frontal cortex which was abuse-specific relative to healthy and psychiatric controls. No group differences in activation were observed for successful inhibition. The participants with a history of abuse exhibited reduced activation in typical dorsal and ventral fronto-striato-thalamo-cerebellar sustained attention regions relative to healthy controls during the most challenging attention condition only, and showed an abuse-specific linear trend of decreasing activation with increasing attention loads in these regions. They also demonstrated abuse-specific hyperactivation of classical fear processing regions of ventromedial prefrontal and anterior cingulate cortices to fearful faces and in fronto-striato-temporo-limbic regions to neutral faces relative to non-maltreated controls. The findings suggest an environmentally triggered disturbance in the normal development of these cognitive and affect networks as a consequence of childhood abuse.

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Lists of Abbreviations

PTSD: Post-Traumatic Stress Disorder

ADHD: Attention Deficit Hyperactivity Disorder

BPD: Borderline Personality Disorder

WCST: Wisconsin Card Sorting Test

TOL: Tower of London

SOC: Stockings of Cambridge

ID/ED: Intra-Dimensional/Extra-Dimensional

GM: Grey Matter

WM: White Matter

HPA: Hypothalamic-Pituitary-Adrenal

ROI: Region-of-Interest

sMRI: Structural Magnetic Resonance Imaging

DTI: Diffusion Tensor Imaging

PFC: Prefrontal Cortex

DLPFC: Dorsolateral Prefrontal Cortex

VLPFC: Ventrolateral Prefrontal Cortex

IFC: Inferior Prefrontal Cortex

OFC: Orbitofrontal Cortex

MPFC: Medial Prefrontal Cortex

vmPFC: Ventromedial Prefrontal Cortex

dmPFC: Dorsomedial Prefrontal Cortex

MDD: Major Depressive Disorder

DID: Dissociative Identity Disorder

GAD: Generalized Anxiety Disorder

ACC: Anterior Cingulate Cortex

PCC: Posterior Cingulate Cortex

ASPD: Antisocial Personality Disorder

FA: Fractional Anisotropy

VBM: Voxel-Based Morphometry

WBA: Whole-Brain Analysis

fMRI: Functional Magnetic Resonance Imaging

PTSS: Post-Traumatic Stress Symptoms

sgACC: Subgenual Anterior Cingulate

CEM: Childhood Emotional Maltreatment

MID: Monetary Incentive Delay

RSFC: Resting-State Functional Connectivity

ERN: Error-Related Negativity

ERP: Event-Related Potential

CECA: Childhood Experience of Care and Abuse

CTQ: Childhood Trauma Questionnaire

SMA: Supplementary Motor Area

SAT: Sustained Attention Task

EPT: Emotion Processing Task

SDQ: Strengths and Difficulties Questionnaires

BDI: Beck's Depression Inventory

SES: Socioeconomic Status

FWE: Family-Wise Error

ANOVA: Analysis of Variance

ANCOVA: Analysis of Covariance

MANOVA: Multivariate Analysis of Variance

BOLD: Blood Oxygen Level Dependent

CHAPTER 1

Childhood Maltreatment and Mental/Physical Health Consequences

Childhood maltreatment is a major public-health and social problem in high-income countries and it is estimated that every year, about 4-16% of children are physically abused, 10% are neglected or psychologically abused and 5-10% are exposed to penetrative sexual abuse (Gilbert et al., 2009). Recent statistics in the United Kingdom show prevalence rates of 6.9% for severe physical abuse, 4.8% for sexual abuse and 9.8% for severe emotional and physical neglect in children (NSPCC, 2011). The seriousness of this problem is further underscored by the 2006 World Health Organization (WHO) report on prevention of childhood maltreatment which exhorted the need for more attention and investment in prevention and epidemiological monitoring that is given to other serious public-health concerns affecting children such as HIV/AIDS, smoking and obesity (Butchart et al., 2006). The report further recommended expansion of the scientific evidence base for the magnitude and effects of this problem (Butchart et al., 2006).

Childhood maltreatment encompasses any act or series of acts of omission or commission by a parent or caregiver that results in harm, potential for harm, or threat of harm to a child, even if harm is not intended (Leeb et al., 2008). Four forms of childhood maltreatment are widely recognized: physical abuse, sexual abuse, emotional/psychological abuse and neglect. Childhood physical abuse is the infliction of injury on the child by a caregiver via various non-accidental means, including hitting with a hand, stick, strap, or other objects; punching; kicking; shaking; throwing; burning; stabbing; or choking (Sedlak and Broadhurst, 1996). Childhood sexual abuse is any sexual act with a child performed by an adult or older

child including intercourse, attempted intercourse, oral-genital contact, fondling of genitals directly or through clothing, exhibitionism, exposing children to adult sexual activity or pornography and the use of the child for prostitution or pornography (Putnam, 2003). In childhood emotional/psychological abuse, the abusers reject, isolate, terrorize, ignore and corrupt their victims (Garbarino and Garbarino, 1994). Emotional/psychological abuse also includes verbal abuse, penalizing a child for positive/normal behaviours and witnessing domestic violence. Finally, neglect is the failure to provide for the child's basic needs including food, shelter, safety and supervision; and may be physical (e.g. lack of health care, abandonment, inadequate supervision), educational (e.g. allowance of chronic truancy, failure to enrol a child in school) or emotional (e.g. inattention to the child's needs for affection, refusal of or failure to provide needed psychological care and permission of drug/alcohol use by the child) (English et al., 2005).

Childhood maltreatment is a common serious problem with long-term detrimental effects on the child's physical and psychological well-being, their normal developmental transition into adulthood, their family and the society at large. The most tragic consequence of childhood maltreatment is the thousands of child death every year due to child homicide or neglect. The WHO estimated that there are 155000 deaths in children younger than 15 years worldwide every year due to abuse or neglect, which is 0.6% of all deaths and 12.7% of deaths due to any injury (Pinheiro, 2006). Childhood maltreatment increases the risks of both internalizing disorders (e.g. anxiety, depression, Post-traumatic stress disorder (PTSD), self-harm and suicide) and externalizing disorders and behavioural problems (e.g. Attention deficit hyperactivity disorder (ADHD), conduct disorder, aggression, antisocial

behaviours, crime and substance abuse) (Fergusson et al., 2008; Lansford et al., 2007), eating disorders (Brewerton, 2007), delinquency (Maas et al., 2008), academic and occupational underachievement (Boden et al., 2007), prostitution (Wilson et al., 2008), teenage pregnancy (Lansford et al., 2007), abortion and sexually transmitted diseases (Senn et al., 2007) as well as physical problems such as obesity (Thomas et al., 2008) and chronic pain in adulthood (Walsh et al., 2007).

Thus, several large-scale epidemiological studies have documented significant associations between adverse childhood experiences including childhood maltreatment and psychopathology in childhood and adulthood (Gilbert et al., 2009; Green et al., 2010; Kessler et al., 2010; Nanni et al., 2011). The National Comorbidity Survey Replication (NCS-R) and the WHO World Mental Health (WMH) Survey Initiative reported that childhood adversities including childhood maltreatment are significantly associated with first onsets of a wide range of psychiatric disorders including mood disorders, anxiety disorders and PTSD over the life course (Green et al., 2010; Kessler et al., 2010; McLaughlin et al., 2010); and eradication of childhood adversities would lead to a reduction of 22.9% in mood disorders, 31% in anxiety disorders, 41.6% in behavioural disorders and 27.5% in substance disorders (Kessler et al., 2010).

In addition, studies show that about 25%-33% of maltreated children meet criteria for major depression by their later 20s and this is more likely with harsh or severe physical abuse than with less severe forms of maltreatment (Fergusson et al., 2008). A meta-analysis further suggested that childhood maltreatment is associated with an elevated risk of developing recurrent and persistent depressive episodes

(odds ratio (OR) = 2.27, 95% confidence interval (CI) = 1.80-2.87) and is associated with a lack of response or remission during treatment for depression (OR = 1.43, 95% CI = 1.11-1.83) (Nanni et al., 2011).

Furthermore, in a recent systematic review and meta-analysis of the long-term health consequences of non-sexual childhood maltreatment (Norman et al., 2012), statistically significant associations were observed between physical abuse, emotional abuse and neglect and **depressive disorders** (physical abuse [OR = 1.54, 95% CI = 1.16-2.04], emotional abuse [OR = 3.06, 95% CI = 2.43-3.85] and neglect [OR = 2.11, 95% CI = 1.61-2.77]), **anxiety disorders** (physical abuse [OR = 1.51, 95% CI = 1.27-1.79], emotional abuse [OR = 3.21, 95% CI = 2.05-5.03] and neglect [OR = 1.82, 95% CI = 1.51-2.20]), **drug abuse** (physical abuse [OR = 1.92, 95% CI = 1.67-2.20], emotional abuse [OR = 1.41, 95% CI = 1.11-1.79] and neglect [OR = 1.36, 95% CI = 1.21-1.54]), **suicide attempts** (physical abuse [OR = 3.40, 95% CI = 2.17-5.32], emotional abuse [OR = 3.37, 95% CI = 2.44-4.67] and neglect [OR = 1.95, 95% CI = 1.13-3.37]) and **sexually transmitted infections and risky sexual behaviours** (physical abuse [OR = 1.78, 95% CI = 1.50-2.10], emotional abuse [OR = 1.75, 95% CI = 1.49-2.04] and neglect [OR = 1.57, 95% CI = 1.39-1.78]). For physical abuse, significant associations were also observed with **childhood behavioural problems and conduct disorder** (OR = 5.98, 95% CI = 2.73-13.1), **eating disorders** (OR = 2.58, 95% CI = 1.50-2.10), **PTSD** (OR = 2.94, 95% CI = 2.25-3.84) and **panic disorder** (OR = 1.69, 95% CI = 1.34-2.13). A dose-response relationship was observed with physical abuse but not with emotional abuse and neglect; with anxiety disorders more likely to be associated with frequent physical abuse than with physical abuse that occurred only sometimes in childhood. There

was also suggestive evidence of a significant association between physical abuse and physical disorders such as arthritis, ulcers and headache/migraine in adulthood.

Therefore, childhood maltreatment is a major risk factor for the development of a host of psychiatric, physical and behavioural problems. The next three chapters will be a literature review on studies that have examined neuropsychological impairments (Chapter 2) as well as brain structural (Chapter 3) and functional abnormalities (Chapter 4) in individuals with a history of childhood maltreatment.

CHAPTER 2

Cognitive and Emotion Processing Deficits in Childhood Maltreatment (Neuropsychological Studies)

Childhood maltreatment has been associated with a range of cognitive deficits including poor IQ and academic performance, impaired inhibitory control, attention, memory, working memory and problem solving as well as emotion and reward processing deficits.

2.1. IQ and Academic Performance

Compared to non-maltreated controls, lower IQ has been found in children who experienced neglect (De Bellis et al., 2009), early institutionalization (Vorria et al., 2006; Loman et al., 2009; Pollak et al., 2010), physical (Carrey et al., 1995; Prasad et al., 2005; Nolin and Ethier, 2007) and sexual abuse (Carrey et al., 1995) but not in adults exposed to childhood maltreatment (Bremner et al., 1995; Twamley et al., 2004); which was furthermore negatively related to the severity of childhood maltreatment (Carrey et al., 1995; De Bellis et al., 2009). There is also some evidence of a dose-response relationship such that children who experienced maltreatment in multiple developmental periods had significantly lower IQ than children maltreated in only one developmental period (Jaffee et al., 2011). However, most of these studies on maltreated children did not control for psychiatric disorders except for the study of De Bellis et al (2009) which found that neglected children with and without PTSD had significantly lower IQ than healthy controls, thereby suggesting that lower IQ is related to maltreatment rather than PTSD.

Early stress such as childhood maltreatment also heightens a child's risk for academic problems (Kaplow et al., 2009). Lower academic performance has been found in children with a history of neglect (Kendall-Tackett and Eckenrode, 1996) and early institutionalization (Loman et al., 2009) as well as in adults with a history of childhood maltreatment (Navalta et al., 2006; Majer et al., 2010). However, only the study of Majer et al (2010) controlled for psychiatric comorbidities while the other studies either did not assess or control for them.

2.2. Inhibitory Control

Compared to healthy controls, children who suffered from neglect, physical and sexual abuse exhibited deficits in motor response inhibition (Mezzacappa et al., 2001; Nolin and Ethier, 2007; DePrince et al., 2009) and had more difficulty inhibiting responses associated with adverse consequences (Mezzacappa et al., 2001). Moreover, unlike healthy controls, the children who had experienced abuse showed diminished improvement with increasing age in the capacity for inhibitory control (Mezzacappa et al., 2001). Adults exposed to childhood sexual abuse also had deficits in inhibitory capacity especially during longer delays between target presentation and stop signal compared to healthy controls (Navalta et al., 2006). One study, however, did not find inhibitory deficits in children who experienced early institutionalization (Loman et al., 2013).

Additionally, maltreated children (DePrince et al., 2009) and children with maltreatment-related PTSD (Beers and de Bellis, 2002) also had poorer cognitive interference control than healthy controls. Moreover, the below average performance of both groups of maltreated children with and without PTSD (which did not differ

significantly from each other) (Samuelson et al., 2010) further suggest that deficits in interference control may be due to abuse and not PTSD.

Hence, these studies suggest that childhood maltreatment is associated with impaired inhibitory control in children which may persist into adulthood; however, more studies in adults who experienced childhood maltreatment are needed. Also, it is worth noting that most of these studies did not measure or control for psychiatric comorbidities (Mezzacappa et al., 2001; Navalta et al., 2006; Nolin and Ethier, 2007; DePrince et al., 2009; Loman et al., 2013) making it difficult to distinguish whether the observed deficits were due to childhood maltreatment or to the psychiatric conditions. Additionally, some studies did not measure or control for drug (Mezzacappa et al., 2001; Nolin and Ethier, 2007; DePrince et al., 2009; Loman et al., 2013) and medication use (Navalta et al., 2006; Nolin and Ethier, 2007; DePrince et al., 2009) and many of the participants in the study of Mezzacappa et al (2001) were on various medications including psychostimulants, antidepressants, mood stabilizers and alpha-2 adrenergic agonists which may have confounded the results.

2.3. Attention

Children exposed to childhood maltreatment, relative to healthy controls, have shown auditory (Nolin and Ethier 2007; DePrince et al., 2009; Bucker et al., 2012) and visual (Nolin and Ethier 2007; De Bellis et al., 2009; Pollak et al., 2010) attention deficits and the visual impairment was furthermore related to increased PTSD symptoms (De Bellis et al., 2009). Also, children with maltreatment-related PTSD (Beer and De Bellis 2002) have shown to commit more omission errors than healthy controls during sustained attention; while institutionalized children had

difficulties sustaining attention (i.e. increased omission errors) compared to non-institutionalized children, which was furthermore related to longer institutional care (McDermott et al., 2012; Loman et al., 2013). In adults, childhood physical abuse and neglect were associated with sustained attention deficits (Gould et al., 2012), although two studies reported negative findings (Twamley et al., 2004; Majer et al., 2010).

Therefore, there is consistent evidence for attention deficits in maltreated children although more studies in adults exposed to childhood maltreatment are needed. However, some of these studies also did not measure or control for psychiatric comorbidities (Beer and De Bellis 2002; Nolin and Ethier, 2007; DePrince et al., 2009; Pollack et al., 2010; Gould et al., 2012; Loman et al., 2013), medication (Nolin and Ethier, 2007; De Bellis et al., 2009; DePrince et al., 2009) or drug use (Nolin and Ethier, 2007; De Bellis et al., 2009; DePrince et al., 2009; Majer et al., 2010; Pollak et al., 2010; Bucker et al., 2012; Gould et al., 2012; Loman et al., 2013) which may have influenced the findings.

2.4. Memory

Many neuropsychological studies in childhood maltreatment have investigated memory functions and reported memory deficits in individuals exposed to childhood maltreatment. For instance, poorer visual memory has been found in children who experienced early institutionalization (Bos et al., 2009; Pollak et al., 2010) and childhood neglect with PTSD (De Bellis et al., 2009) compared to non-maltreated controls. Furthermore, neglected children with PTSD also performed worse than neglected children without PTSD (De Bellis et al., 2009); while

childhood maltreatment-related PTSD symptoms were strongly associated with lower visual memory performance (De Bellis et al., 2010). Similarly, poorer verbal memory has been reported in children and adolescents with maltreatment-related PTSD than non-maltreated controls (Beers and De Bellis, 2002) and in children with PTSD due to witnessing domestic violence than those who were also exposed to domestic violence but did not develop PTSD (Samuelson et al., 2010); thereby suggesting that memory deficits in maltreated children may be related to their PTSD symptoms.

Likewise, adults with a history of childhood maltreatment had poorer visual memory than healthy controls (Navalta et al., 2006; Gould et al., 2012; Syal et al., 2014), which was furthermore related to the duration of childhood sexual abuse (Navalta et al., 2006). Visual memory deficits also correlated with more exposure to emotional abuse and physical neglect in healthy adults (Majer et al., 2010) and with severity of childhood sexual abuse in a large study of 225 adults with various psychiatric diagnoses including depression and borderline personality disorder (BPD) (Savitz et al., 2007). In addition, poorer verbal memory was found in adults with a history of childhood sexual and physical abuse compared to healthy controls (Bremner et al., 1995) and in women with childhood sexual abuse-related PTSD compared to women who had experienced childhood abuse but without PTSD and healthy controls (Bremner et al., 2004) which was furthermore correlated with severity of childhood abuse (Bremner et al., 1995, 2004) and increased PTSD symptoms (Bremner et al., 2004). Nevertheless, there are also studies that found no association between memory impairment and maltreatment in children (Nolin and Ethier, 2007) or adults (Stein et al., 1999; Pederson et al., 2004; Jelici et al., 2008).

Thus, there is evidence for visual and verbal memory deficits in maltreated children and adults and the evidence further suggests that the deficits in maltreated children may possibly be associated with PTSD symptoms while the deficits in adults may be related to both childhood maltreatment and psychopathology. But again, many of the above studies did not measure or control for psychiatric comorbidities (Bremner et al., 1995; Stein et al., 1999; Beers and De Bellis 2002; Navalta et al., 2006; Jelicic et al., 2008; Bos et al., 2009; Pollak et al., 2010; Gould et al., 2012), medication (Bremner et al., 1995; Pederson et al., 2004; Navalta et al., 2006; Savitz et al., 2007; Jelicic et al., 2008; Bos et al., 2009; De Bellis et al., 2009, 2010) or drug use (Savitz et al., 2007; Jelicic et al., 2008; Bos et al., 2009; De Bellis et al., 2009; Majer et al., 2010; Pollak et al., 2010; Gould et al., 2012; Syal et al., 2014) which may have confounded the findings.

2.5. Working Memory

Similarly, working memory deficits have been frequently reported in children who experienced childhood maltreatment (DePrince et al., 2009; Samuelson et al., 2010; Bucker et al., 2012; Augusti et al., 2013) and early institutionalization (Bos et al., 2009; Pollack et al., 2010) relative to their non-maltreated peers. In adults, greater exposure to childhood emotion abuse, physical neglect (Majer et al., 2010) and sexual abuse (Gould et al., 2012) were associated with greater working memory impairment but two studies reported no deficits in maltreated adults compared to non-maltreated controls (Pedersen et al., 2004; Twamley et al., 2004). However, except for the studies of Majer et al (2010) and Bucker et al (2012) on healthy maltreated individuals and the study of Twamley et al (2004) that included a group with a history of childhood abuse but without PTSD, all other studies did not assess

or control for psychiatric comorbidities. Some studies also did not control for the confounding effects of medication (Pederson et al., 2004; Bos et al., 2009; DePrince et al., 2009; Augusti et al., 2013) and drug use (Bos et al., 2009; DePrince et al., 2009; Majer et al., 2010; Pollak et al., 2010; Bucker et al., 2012; Gould et al., 2012; Augusti et al., 2013).

2.6. Other Executive Functions

Some studies in childhood maltreatment also examined other executive functions using neuropsychological tests such as the Wisconsin Card Sorting Test (WCST), Tower of London (TOL), Stockings of Cambridge (SOC) and the intra-extra dimensional shift set (ID/ED) test. The WCST assesses executive functions involved in complex cognitive activities such as cognitive flexibility, problem solving, rule-learning, processing new information, generating strategies, sequencing complex actions and self-regulating thought. The TOL assesses planning, control, self-regulation and problem-solving abilities. The SOC measures spatial planning and problem solving. The ID/ED test measures rule acquisition, set shifting and manipulation through reversal.

On the WCST, children with maltreatment-related PTSD (Beers and De Bellis, 2002) and adults exposed to childhood maltreatment but without PTSD (Twamley et al., 2004) performed significantly worse than healthy controls. Furthermore, the WCST scores were in the below average range for both groups of maltreated children with and without PTSD (which did not differ significantly from each other) (Samuelson et al., 2010) and were associated with physical abuse and neglect in healthy adolescents (Spann et al., 2012); thereby suggesting that poorer

performance on WCST may be related to exposure to childhood maltreatment regardless of PTSD. On the TOL, children who were neglected and physically abused (Nolin and Ethier, 2007) and neglected with PTSD (De Bellis et al., 2009) obtained lower scores than healthy controls. The TOL scores were again in the below average range for both groups of maltreated children with and without PTSD (Samuelson et al., 2010). Finally, childhood maltreatment was associated with poorer performance on the SOC and ID/ED tests in adults compared to healthy controls (Gould et al., 2012); but a few studies reported negative findings in maltreated children (Bos et al., 2009; Pollak et al., 2010; Augusti et al., 2013) and in healthy adults with a history of childhood maltreatment (Majer et al., 2010). Finally, using the Hayling test that assesses initiation, planning and cognitive flexibility, adolescents who suffered multitype maltreatment performed worse than their non-maltreated peers (Mothes et al., 2014).

Hence, these studies suggest that maltreated children and adolescents may have difficulties with executive functions including cognitive flexibility, planning, problem solving and self-regulation but more studies are still needed especially in adults who suffered from childhood maltreatment. Yet again, some studies did not measure or control for psychiatric comorbidities (Beers and De Bellis, 2002; Bos et al., 2009; Pollak et al., 2010; Gould et al., 2012; Augusti et al., 2013; Mothes et al., 2014), medication (Nolin and Ethier, 2007; Bos et al., 2009; De Bellis et al., 2009; Augusti et al., 2013; Mothes et al., 2014) or drug use (Nolin and Ethier, 2007; Bos et al., 2009; De Bellis et al., 2009; Pollak et al., 2010; Majer et al., 2010; Spann et al., 2012; Gould et al., 2012; Augusti et al., 2013; Mothes et al., 2014) which could have affected the findings.

2.7. Emotion Processing

The ability to accurately recognize facial expressions of emotion, usually mastered by the preschool years, is necessary for the normal development of adaptive functioning (Izard and Harris, 1995). Maltreated children generally live in stressful environments where negative emotions are highly salient. The development of an increased sensitivity to negative emotions such as anger and fear may be particularly adaptive if it is associated with imminent danger. Indeed, a series of studies by Pollak and colleagues suggest that physically abused children do not have global deficits in emotion recognition or affective information-processing but rather, display differential processing of emotions that is more sensitive to negative valence emotions particularly anger and fear as they are more likely witness anger and to experience fear (Pollak et al., 1997, 2000, 2001; Pollak and Kistler, 2002; Pollak and Sinha, 2002; Pollak and Tolley-Schell, 2003).

Furthermore, the type of maltreatment may also affect the ability to identify and discriminate emotions. For example, children who experienced neglect (Pollak et al., 2000) and early institutionalization (Wisner-Fries and Pollak, 2004; Pears et al., 2005; Vorria et al., 2006) had more difficulties discriminating between various emotions such as angry, sad, fearful and happy facial expressions than healthy controls; whereas physically abused children perceived more distinction between anger and other negative emotional expressions than did neglected children (Pollak et al., 2000).

Besides Pollak's group, other studies have also been conducted to examine attention bias and deficits in facial emotion recognition in maltreated children (Pine

et al., 2005; Masten et al., 2008; Koizumi et al., 2014). For instance, attention bias *away* from angry/threatening expressions was associated with severity of physical abuse and diagnosis of PTSD in children; however, since a large majority of maltreated children had a history of PTSD, it is unclear if attention bias relates specifically to PTSD as opposed to physical abuse, independent of PTSD symptoms (Pine et al., 2005). Although the finding is in contrast with earlier studies by Pollak and colleagues who reported attention bias *towards* angry faces, they did not assess and examine associations with concurrent psychopathology such as PTSD, which may be associated with a bias away from angry traumatizing faces. In addition, studies reported that maltreated children responded faster when identifying fearful but not happy expressions (Masten et al., 2008) and were less accurate in the identification of positive but not negative emotions (Koizumi et al., 2014) compared to non-maltreated children.

There are much fewer studies on emotion processing in adults exposed to childhood maltreatment than in maltreated children (Gibb et al., 2009; Fani et al., 2011; Caldwell et al., 2014). Similar to children who had experienced abuse, adults who were maltreated as children also exhibited preferential attention to angry faces and increased sensitivity in the detection of angry expressions at lower levels of emotional intensity (Gibb et al., 2009). However, attentional bias toward happy and not threatening faces was found to mediate the relationship between childhood maltreatment and PTSD avoidance and numbing symptoms in adults; thereby suggesting that the selective attention towards happy cues may reflect avoidance tendencies rather than hyperattention to positive cues (Fani et al., 2011). Finally, using a facial identification Stroop task, women with high levels of childhood

maltreatment were especially impaired in emotional conflict adaption during incongruent trials preceded by a fearful face incongruent trial compared to women with low levels of childhood maltreatment although both groups adapted similarly to congruent-trial conflict (Caldwell et al., 2014).

Therefore, there is consistent evidence that maltreated children are impaired in emotion processing especially for negative valence emotions such as anger and fear while neglected children are more likely to have difficulties discriminating between various emotional expressions. Adults exposed to childhood maltreatment also showed heightened sensitivity to angry and fearful faces, which is consistent with the findings in maltreated children; however, more studies in adults exposed to childhood maltreatment are needed. Furthermore, none of the above studies measured or controlled for psychiatric comorbidities, medications and drug abuse except for a few studies that excluded participants who reported taking illicit substances (Caldwell et al., 2014) or psychotropic medications (Pollak et al., 2001; Pollak and Tolley-Schell, 2003; Caldwell et al., 2014).

2.8. Reward Processing

Maltreated children also showed impairments in reward-processing and reward-related decision-making tasks. For instance, compared to non-maltreated controls, maltreated children selected risky options faster (Guyer et al., 2006) and made more risky choices in order to avoid losses rather than to achieve gains (Weller and Fisher, 2012). Whereas non-maltreated children responded faster as the chance of winning increased, maltreated children did not vary their response speed as a function of the likelihood of winning which may suggest a reduced sensitivity to

different reward values in the maltreated children (Guyer et al., 2006). The maltreated children were also less likely to adjust their decision making in response to greater potential losses than non-maltreated children (Weller and Fisher, 2012). However, these two studies also did not examine or control for psychiatric comorbidities, medications and drug abuse.

2.9. Conclusions

In summary, there is evidence of lower IQ and poorer academic performance particularly in maltreated children with some evidence that they are related to the abuse experience. Additional, childhood maltreatment is associated with deficits in inhibitory control, attention, working memory and other executive control functions including planning, cognitive flexibility, problem-solving and decision-making. These functions are known to develop late in adolescence and to improve from childhood to adulthood due to progressively linear increasing activation with increasing age in the late developing underlying lateral fronto-striato-cerebellum and fronto-parietal networks (Rubia et al., 2006, 2007, 2010, 2013; Christakou et al., 2009; for review see Rubia, 2013). Hence, the deficits observed may suggest an environmentally triggered disturbance in the normal development of these networks as a consequence of childhood maltreatment. There is also evidence for visual and verbal memory deficits in maltreated children and adults where the deficits seen in maltreated children may possibly be associated with PTSD symptoms. Memory deficits may be due to a disruption of the normal development of underlying neural networks including the hippocampus, amygdala, dorsolateral prefrontal cortex and striatum (McGaugh, 2000). Finally, there is strong evidence of impaired emotion processing of negative valence emotions particularly anger and fear, and also some

evidence of reward processing deficits in maltreated children which may be related to a disruption of the normal development of fronto-limbic neural circuits including the amygdala, ventromedial and orbital prefrontal cortices, anterior cingulate cortex, ventral striatum, insula and cerebellum (Ochsner and Gross, 2005). The next chapter and Chapter 6 examine in greater details the brain structures and networks that are affected and compromised in childhood maltreatment.

CHAPTER 3

Brain Structural Abnormalities in Childhood Maltreatment (Structural MRI and Diffusion Tensor Imaging Studies)

Individual differences in social, behavioural and cognitive functioning result from a combination of genetic and environmental influences on brain development. Development of the brain, a highly plastic organ, is regulated by genes but sculpted by environmental experiences (Lenroot and Giedd, 2008). Although experiential influences can affect brain structure and function throughout the life span, early childhood experience may be particularly crucial. The human brain continues its development during childhood through processes of synaptic remodelling, activity dependent myelination and programmed cell death, which affect both grey matter (GM) and white matter (WM) organization (de Graaf-Peters and Hadders-Algra, 2006). Longitudinal structural imaging studies show that WM increases linearly with age peaking at around age 45 and the increase is most pronounced between childhood and adolescence (Sowell et al., 2003, 2007). GM undergoes substantial non-linear changes, with an increase up to age 10, thought to be due to glial cell proliferation, dendritic and axonal branching; and a decrease after age 10 due to synaptic pruning and myelination (Sowell et al., 2003, 2007). Hence, early stress and exposure to traumatic events such as childhood maltreatment may adversely affect the nature and trajectory of normal brain development (Pechtel and Pizzagalli, 2010).

Childhood maltreatment acts as a severe stressor that produces a cascade of physiological and neurobiological changes ranging from alterations in the hypothalamic-

pituitary-adrenal (HPA) axis to changes in neuroanatomy and neurotransmitter levels , which lead to enduring alterations in the patterns of brain development (Teicher et al., 2006). Thus, childhood maltreatment can affect numerous brain structures and functions that, in turn affects human behaviour and cognition (McCrory et al., 2010). This chapter reviews the effects of childhood maltreatment on brain GM abnormalities in region-of-interest (ROI) studies using structural magnetic resonance imaging (sMRI) (Section 3.1) and WM tract abnormalities using diffusion tensor imaging (DTI) (Section 3.2). Studies using whole-brain based analyses and a meta-analysis of these studies will be presented in Chapter 6. Please refer to Tables 3.1 & 3.2 for a summary of the design and characteristic of sMRI and DTI studies in childhood maltreatment, respectively.

3.1. Childhood Maltreatment and GM Abnormalities: ROI Studies

3.1.1. Cerebral Cortex

The Prefrontal Cortex

The prefrontal cortex (PFC) is extensively interconnected with other cortical and subcortical brain regions and plays a critical role in higher-order control processes that implement a top-down regulation of cognition, behaviour and emotion (Davidson et al., 2000; Ochsner and Gross, 2005; Petrides, 2005). It can be subdivided into three anatomically distinct regions; namely the dorsolateral prefrontal cortex (DLPFC), the ventrolateral prefrontal cortex (VLPFC) including the inferior prefrontal cortex (IFC) and orbitofrontal cortex (OFC) as well as the medial prefrontal cortex (MPFC). In particular, regions that regulate emotion are situated ventrally and medially, and regions that regulate thought and action are situated more dorsally and laterally (Arnsten, 2009).

The DLPFC has extensive connections with sensory and motor cortices and is involved in executive functions such as performance monitoring and manipulation of information in working memory, planning, cognitive flexibility, attention and temporal structuring of goal-directed behaviour (Petrides, 2005). The VLPFC, in interaction with the posterior association areas, also subserves the expression of various executive processes such as active selection, comparison and encoding of information held in short-term and long-term memory as well as response and interference inhibition, attention and timing (Petrides, 2005; Badre and Wagner, 2007).

The MPFC has major connections with the cingulate cortex, retrosplenial areas, temporal pole, superior temporal gyrus and parietotemporal cortex (Amodio and Frith, 2006). It is involved in social cognition, conflict monitoring, error monitoring and response selection (Amodio and Frith, 2006). Particularly, the ventromedial prefrontal cortex (vmPFC) has extensive connections with subcortical limbic structures (amygdala, nucleus accumbens and hypothalamus) that generate emotional responses and thus plays a role in regulating emotional responses (Amodio and Frith, 2006). The dorsomedial prefrontal cortex (dmPFC) has been associated with error monitoring (Modirrousta and Fellows, 2008) and introspection which involves recollection, self-reflection and evaluation (Schmitz and Johnson, 2007). It is also essential for the regulation of autonomic and neuroendocrine stress response and arousal associated with emotional states and behaviour (Radley et al., 2008). It has been further proposed that social cognition tasks, which involve self-knowledge, person perception and mentalizing, activate the anterior region of the MPFC; while cognitive tasks such as action monitoring and attention activate the posterior region (Amodio and Frith, 2006).

The PFC is one of the brain regions that undergoes major developmental changes during childhood and adolescence and may be especially vulnerable to the effects of stress during this developmental period (Lupien et al., 2009). Indeed, several studies found smaller PFC GM volumes in children and adolescents with childhood maltreatment-related PTSD (De Bellis et al., 2002a) and in children (De Brito et al., 2013) and adults (Andersen et al., 2008; Van Harmelen et al., 2010; Carballedo et al., 2012; Morandotti et al. 2013) with a history of childhood maltreatment compared to (healthy) controls. However, two studies reported larger PFC GM volumes (Carrion et al., 2001; Richert et al., 2006) and one study found no significant differences (De Bellis et al., 1999) in children and adolescents with childhood maltreatment-related PTSD compared to healthy controls. One study found larger right dmPFC and left OFC GM volumes in adults who experienced childhood maltreatment compared to those without a history of childhood maltreatment (Chaney et al., 2013).

For instance, healthy maltreated children had significantly smaller medial OFC GM volume (De Brito et al., 2013) while children and adolescents with childhood maltreatment-related PTSD had smaller PFC GM and WM volumes (De Bellis et al., 2002a) compared to healthy controls. In adult studies, individuals exposed to childhood emotional maltreatment showed smaller GM volumes in the left DLPFC, MPFC (Carballedo et al., 2012) and dmPFC (van Harmelen et al., 2010) compared to their non-maltreated counterparts. Women with a history of childhood sexual abuse had significantly smaller PFC GM volume than healthy controls and the PFC volume was found to be particularly sensitive to the adverse effect of childhood sexual abuse at ages 14-16 years (Andersen et al., 2008). Finally, right VLPFC GM volume was significantly

reduced in female BPD patients with a history of childhood maltreatment in comparison to non-maltreated BPD patients; although the result should be interpreted with caution due to the smaller sample size (Morandotti et al., 2013).

Furthermore, two studies reported direct correlations between brain abnormalities and measures of childhood abuse. Left middle frontal GM volume was negatively correlated with childhood sexual abuse severity in adult psychosis patients (Sheffield et al., 2013) and MPFC volume reductions were related to higher frequency of childhood emotional maltreatment (van Harmelen et al., 2010).

However, two studies found that children with childhood maltreatment-related PTSD had significantly larger volumes of GM in the left frontal lobe (Carrion et al., 2001) and middle-inferior and ventral regions of the PFC (Richert et al., 2006) than healthy controls. There was also a significant negative correlation between dorsal PFC GM volume and functional impairment in social functioning, school performance, general distress and experience of regressive behaviours (Richert et al., 2006).

In summary, adults who had experienced childhood maltreatment seem to have reduced GM volumes in the DLPFC, VLPFC and MPFC regions while the findings on children and adolescent samples are more inconsistent. Moreover, the majority of the studies on childhood maltreatment-related brain structural abnormalities above examined maltreated participants with psychiatric comorbidities which make it difficult to isolate the unique effect of childhood maltreatment since the abnormalities reported

could be associated with the comorbid psychiatric disorder(s), childhood maltreatment or both.

The Temporal Cortex

The temporal lobe can generally be divided into two regions: dorsolateral and ventromedial temporal lobe. The dorsolateral region supports cognitive functions associated with several sensory systems such as auditory and language processing. The ventromedial region, which contains major portions of the limbic system, is associated with memory and emotion processing. In particular, the superior temporal gyrus is involved in auditory processing, speech comprehension (Leff et al., 2009) and social cognition (Campanella and Belin, 2007). The temporal pole covers the anterior aspect of the temporal lobe and has strong connection with the amygdala and OFC. It is believed to be important in social cognition such as conceptual knowledge of social behaviours (Zahn et al., 2007), moral cognition (Moll et al., 2005), social-emotional functions including theory of mind (Ross and Olson, 2010) and socially relevant memory (Simmons et al., 2010).

There are mixed findings from studies that examined the temporal lobe in individuals exposed to childhood maltreatment. Some studies found that maltreated individuals had smaller (De Bellis et al., 2002a; De Brito et al., 2013), larger (Bremner et al., 1997; De Bellis et al., 2002b), or equivalent (De Bellis et al., 1999, 2001; Carrion et al., 2001; Vythilingham et al., 2002) temporal lobe GM volumes compared to healthy controls.

For instance, children and adolescents with childhood maltreatment-related PTSD had smaller GM volume in the right temporal lobe (De Bellis et al., 2002a); while healthy maltreated children had smaller GM volumes in the bilateral middle temporal, left inferior temporal and right superior temporal gyri (De Brito et al., 2013) relative to healthy controls. However, some children and adolescents with childhood maltreatment-related PTSD have also been found to have larger total and mainly right-hemispheric superior temporal GM volumes than healthy controls (De Bellis et al., 2002b). There were also a more pronounced right > left asymmetry in total and posterior superior temporal GM volumes, but a loss of the left > right asymmetry in total, anterior and posterior superior temporal GM volumes in maltreated PTSD patients compared to healthy controls (De Bellis et al., 2002b). Adults with childhood maltreatment-related PTSD also had significantly larger left temporal lobe GM volume than healthy controls (Bremner et al., 1997).

In summary, findings of childhood maltreated-related GM abnormalities in temporal lobe regions are largely inconsistent and most of the studies examined patients with childhood maltreatment-related PTSD except for the studies of De Brito et al (2013) who used healthy maltreated children and Vythilingam et al (2002) who included a psychiatric control group of major depressive disorder (MDD) patients in addition to a group of MDD patients with a history of childhood maltreatment and a healthy control group. Hence, most of the findings above are again limited by the association of the comorbid psychiatric disorder(s) with the childhood maltreatment experience.

The Parietal Cortex

The anterior parietal cortex is concerned with somatosensory sensations. The posterior parietal cortex has long been associated with attentional control, spatial perception, movement planning and control, multisensory integration, working memory (Corbetta and Shulman, 2002) and also episodic memory (Cabeza et al., 2008). The posterior parietal cortex, which has connections with many brain regions including the PFC, temporal cortex and hippocampal regions, can also be subdivided into dorsal and ventral regions (usually known as the dorsal and ventral parietal cortex, respectively). Corbetta and Shulman (2002) proposed an influential cognitive-neuroscience model of attention whereby the dorsal parietal cortex together with the dorsal frontal regions (dorsal frontoparietal system) is associated with top-down attention; while the ventral parietal cortex together with the ventral frontal regions (ventral frontoparietal system) is associated with bottom-up attention. They posited that the dorsal parietal lobule and parts of the intraparietal sulcus are involved in the deployment of attention and response selection; whereas the ventral regions, specifically the temporoparietal junction, are involved in the detection of behaviourally relevant and novel stimuli. Furthermore, some studies found that within attentional control, shifting attention is mediated by the dorsal parietal lobule and sustained attention is mediated by the more lateral and ventral parietal regions (Malhotra et al., 2009; Thakral and Slotnick, 2009).

Early adverse stress such as childhood maltreatment heightens a child's risk for attention and academic problems (Kaplow et al., 2009). Only one study examined the volumes of the parietal region and reported no significant differences in the parietal lobe

GM volume between children with childhood maltreatment-related PTSD and healthy controls (Carrion et al., 2001).

The Occipital Cortex

The occipital lobe is positioned at the posterior region of the human cerebral cortex and is the main centre for visual processing. It consists of the primary visual cortex (striate cortex) as well as the secondary and tertiary visual areas (extrastriate visual cortex), which represent the visual association area of the occipital lobe (Clark et al., 2010). Only one study, on intimate partner violence, reported an association between smaller occipital GM volume and childhood maltreatment (Fennema-Notestine et al., 2002).

3.1.2. The Limbic System

Hippocampus

The hippocampus occupies a central position in the limbic system and is generally known for its role in declarative memory (Manns and Eichenbaum, 2006). It is also implicated in conditioning and extinction of fear responses and may be involved in the context processing of fear (Phillips and LeDoux, 1992). The hippocampus is implicated in both cognitive and emotional processes: cognitive information enters the hippocampus via the entorhinal cortex while information related to the emotional state arrives from the septum, amygdala, hypothalamus and brainstem (Witter et al., 2000). The hippocampus exerts strong regulatory control on the HPA axis and it is believed that hippocampal lesions impair control of the hormonal stress response (Dedovic et al.,

2009); while elevations of stress hormones lead to hippocampal dysfunction (Herman et al., 2005).

As such, the glucocorticoid receptor-rich hippocampus has been one of the most commonly examined ROIs in studies on the neural effects of traumatic stress such as childhood maltreatment. In adult studies, smaller hippocampal volume has been reported in women with a history of childhood sexual abuse (Stein et al., 1997; Andersen et al., 2008), in healthy adults at family risk for depression and with a history of childhood emotional abuse (Carballedo et al., 2012), and in those with childhood maltreatment-related psychiatric disorders such as PTSD (Bremner et al., 1997, 2003; Kitayama et al., 2005; Weniger et al., 2008; Thomaes et al., 2010), dissociative identity disorder (DID) (Vermetten et al., 2006), MDD (Vythilingam et al., 2002; Chaney et al., 2013) and BPD (Driessen et al., 2000; Schmahl et al., 2003) compared to healthy controls; where the left hippocampal volume was furthermore negatively correlated with the duration of childhood maltreatment (Bremner et al., 1997). Moreover in healthy adults, the hippocampal GM volume correlated negatively with childhood maltreatment (Dannlowski et al., 2012a) and in men, but not women, with childhood emotional abuse (Samplin et al., 2013). Childhood maltreatment was also associated with volume reductions in hippocampal subfields containing the (cornu ammonis) (CA) and dentate gyrus (DG) particularly the CA4-DG, CA2-CA3, subiculum, presubiculum and CA1 in adults (Teicher et al., 2012). Additionally, the hippocampal volume was found to be particularly sensitive to the adverse effect of childhood sexual abuse at ages 3-5 years and ages 11-13 years (Andersen et al., 2008).

However, there are also studies in adults with a history of childhood maltreatment (Cohen et al., 2006; van Harmelen et al. 2010) and adults with childhood maltreatment-related psychiatric disorders such as PTSD (Pederson et al., 2004) and psychotic disorder (Sheffield et al., 2013) that reported negative findings.

Two studies compared women with childhood maltreatment-related PTSD with women without PTSD and healthy controls (Pederson et al., 2004; Bremner et al., 2003) but had different findings. This could possibly because in the study of Pederson et al (2004), the females were on average 10 years younger with milder PTSD symptomology, had a history of childhood physical and emotional abuse besides sexual abuse, were not evaluated for other Axis 1 psychiatric disorders and medication use, and also whole brain volume measurement was not taken to control for possible brain volume differences.

It is worth noting that the smaller left hippocampal volume in women with MDD found in the study of Vythilingam et al (2002) was observed exclusively in those who had a history of childhood maltreatment, as the bilateral hippocampal volumes in the depressed women without a history of childhood maltreatment were similar to those of the healthy controls. Similarly, smaller hippocampal volume was found in MDD patients who experienced childhood maltreatment than in MDD patients who did not (Chaney et al., 2013). Likewise, in the study of Bremner et al (2003), women with PTSD and a history of childhood sexual abuse had significantly smaller bilateral hippocampal volumes than both the maltreated women without PTSD and healthy controls. Hence,

volume loss in the hippocampus during adulthood may possibly be a feature of psychiatric disorders related to childhood maltreatment.

On the other hand, hippocampus abnormalities have not been observed in most studies in maltreated children and adolescents (Tupler and De Bellis, 2006; Mehta et al., 2009a; Tottenham et al., 2010; De Brito et al., 2013), children and adolescents with childhood maltreatment-related PTSD (De Bellis et al., 1999, 2001, 2002a; Carrion et al., 2001; Woon and Hedges, 2008) and adolescent with generalized anxiety disorder (GAD) (Liao et al., 2013) compared to healthy controls. Woon and Hedges (2008) in their meta-analysis concluded that reduced bilateral hippocampal volumes were found in adults with childhood maltreatment-related PTSD compared to healthy controls, but this deficit was not seen in children with maltreatment-related PTSD; suggesting that hippocampus abnormalities may not manifest until adulthood. In support of this neurotoxicity hypothesis, Carrion et al (2007) reported that PTSD symptoms and cortisol at baseline predicted hippocampal reduction over a 12-to 18-months interval in maltreated children with PTSD. Also, a recent prospective longitudinal study found that childhood maltreatment during early adolescence was associated with a decrease in the normal pattern of growth of the left hippocampus from early to mid-adolescence indirectly through the experience of psychopathology (Whittle et al., 2013).

Furthermore, four meta-analysis studies of hippocampal volume in adult PTSD patients reported significantly smaller hippocampal volumes in PTSD patients compared to both trauma-unexposed controls and trauma-exposed controls without PTSD (Kitayama et al., 2005; Smith, 2005; Karl et al., 2006; Woon et al., 2010). Trauma-

exposed controls without PTSD had reduced bilateral hippocampal volumes compared to trauma-unexposed controls (Smith, 2005; Karl et al., 2006; Woon et al., 2010) suggesting that trauma exposure itself may be associated with hippocampal volume deficits. Nonetheless, the findings of reduced right (Kitayama et al., 2005; Smith, 2005; Woon et al., 2010) and left (Kitayama et al., 2005; Smith, 2005; Karl et al., 2006) hippocampal volumes in PTSD patients relative to trauma-exposed controls without PTSD may also raise the possibility that the development of PTSD involves an additional neuropathological process beyond that associated with trauma exposure (Woon et al., 2010).

Amygdala

The amygdala is a nucleus complex located in the anterior medial portion of the temporal lobe. It receives sensory information from advanced levels of visual, auditory and somatosensory cortices, and from the olfactory system, insular cortex, perirhinal cortex, parahippocampal gyrus and the multimodal sensory areas of the frontal lobe (Stefanacci and Amaral, 2002). Output from the amygdala is projected to a wide range of target structures such as the PFC, striatum, sensory cortices, hippocampus, basal forebrain and other subcortical structures responsible for autonomic responses (Stefanacci and Amaral, 2002). Its close ties with the hippocampus help form memories between sensory cues and emotions, and simultaneous activation of both the amygdala and hippocampus is important in memory formation and recall (Milad et al., 2007).

The amygdala is mostly involved in emotional processing (Phelps and Ledoux, 2005), behavioural regulation (Dolans, 2007), fear conditioning (Adolphs et al., 2005)

and emotion-related memories (LaBar and Cabeza, 2006). It appears to have a predominant role in negative emotions and in coding emotional intensity as well as emotional valence (Bertson et al., 2007). Although the amygdala is most often discussed in the context of emotional processes, the amygdala and its extensive interconnections with the PFC (especially the posterior OFC) and the anterior cingulate cortex likely underlie many aspects of the interactions between emotional and cognitive processes such as reinforcement learning (Salzman and Fusi, 2010).

There are mixed findings from studies that examined the amygdala in individuals with a history of childhood maltreatment: two studies found larger amygdala volumes in institutionalized children (Tottenham et al., 2010) and adolescents (Mehta et al., 2009a) that had experienced severe early caregiver deprivation, a form of emotional maltreatment or neglect, than healthy controls. Some studies reported smaller amygdala volumes in women with childhood maltreatment-related psychiatric disorders such as PTSD (Weniger et al., 2008), DID (Vermetten et al., 2006) and BPD (Driessen et al., 2000; Schmahl et al., 2003); while others found no significant differences in children and adolescents (De Bellis et al., 1999, 2001, 2002a; Carrion et al., 2001; Woon and Hedges, 2008) and adults (Bremner et al., 1997) with childhood maltreatment-related PTSD, in adolescents with GAD (Liao et al., 2013), in adults with a history of childhood sexual abuse (Andersen et al., 2008; Sheffield et al., 2013) and emotional maltreatment (van Harmelen et al., 2010), as well as in healthy maltreated children (De Brito et al., 2013) and healthy adults with early life stress including childhood maltreatment (Cohen et al., 2006), compared to (healthy) controls.

Furthermore, two studies reported direct correlations between brain abnormalities and measures of abuse. For instance, in adolescents with severe deprivation, the left amygdala volume was negatively correlated with the time spent in institutions thereby indicating that the amygdala may be sensitive to the deprivation experienced (Mehta et al., 2009a). Children who were adopted later had significantly larger amygdala volume than the early adopted group and healthy controls and this was however associated with longer length of orphanage stay, poorer emotion regulation and increased anxiety (Tottenham et al., 2010).

It is worth noting that the smaller amygdala volume in the above-mentioned studies were mostly seen in female adult patients with childhood maltreatment-related psychiatric disorders such as PTSD, DID and BPD; while no significant differences were found in children and adolescents with childhood maltreatment-related PTSD compared to healthy controls (De Bellis et al., 1999, 2001, 2002a; Carrion et al., 2001). Woon and Hedges (2008) in their meta-analysis found that the amygdala volume in children with maltreatment-related PTSD did not differ from that of healthy controls. Interestingly, women with a history of childhood maltreatment but without DID had larger amygdala volume than healthy controls and the authors further postulated that larger amygdala volume may be protective in the face of early trauma (Vermetten et al., 2006). In addition, a recent prospective longitudinal study reported that higher levels of childhood maltreatment were associated with a decrease in the left amygdala development from early to mid-adolescence (Whittle et al., 2013). Thus, smaller amygdala volume may be due to childhood maltreatment-related psychiatric disorders such as PTSD, DID, BPD developed in adulthood (especially in females) and/or

reduction in volume may possibly manifest later in life. Nonetheless, more studies are needed to examine the effects of childhood maltreatment on the amygdala volume in children and adolescents with and without comorbid psychiatric disorders.

Cingulate Cortex

The cingulate cortex can be subdivided into four parts: the anterior cingulate cortex (ACC) (pregenual anterior cingulate cortex and subgenual cingulate cortex), the mid-cingulate cortex, the posterior cingulate cortex (PCC) and the retrosplenial cortex. The ACC receives extensive input from the amygdala and controls the relationship between the emotional limbic system and the autonomic portions of the nervous system. It is involved in the appreciation and expression of emotions and storage of emotional memories (Vogt, 2005), error detection and conflict monitoring (Kerns et al., 2004) and shifting attention during working memory (Kondo et al., 2004). The mid-cingulate cortex also receives inputs from the amygdala and registers emotional sensations but it projects mainly to the motor areas and regulates skeletomotor function. It is part of the medial pain system and is involved in the affective and/or cognitive dimensions of pain processing (Vogt, 2005). Furthermore, this region may also be engaged in cognitive tasks that do not necessarily require movement and is involved in decision making processes on the basis of the reward value of anticipated outcome of a particular motor response (Bush et al., 2002). The PCC, which receives substantial input from the hippocampus formation (Kobayashi and Amaral, 2003), is involved in visuospatial orientation in response to somatosensory input (Vogt, 2005) and is important in successful retrieval of autobiographic memories (Maddock et al., 2001). Finally, the retrosplenial cortex seems to play a role in memory access mostly for valenced

information, and probably contributes to the functions of the PCC (Vogt, 2005); which together form part of the default mode network (Buckner et al., 2008).

Several studies reported smaller ACC GM volumes in adults with childhood maltreatment-related PTSD (Kitayama et al., 2006; Thomaes et al., 2010) and in healthy adults exposed to childhood maltreatment (Cohen et al., 2006; Carballedo et al., 2012) compared to healthy controls. For instance, adult patients with childhood maltreatment-related PTSD had significantly smaller right ACC GM volume than healthy controls (Kitayama et al., 2006; Thomaes et al., 2010) and the right dorsal ACC GM volume correlated negatively with the severity of childhood maltreatment (Thomaes et al., 2010). Healthy adults with more than two adverse childhood events including childhood maltreatment (Cohen et al., 2006) and who experienced childhood emotional abuse (Carballedo et al., 2012) had smaller ACC GM volume than healthy controls. Finally, ACC volume was inversely correlated with a history of childhood sexual/physical abuse in adult MDD patients (Treadway et al., 2009) and violent adults patients (antisocial personality disorder (ASPD) and violent schizophrenia) (Kumari et al., 2014).

In summary, the findings suggest that childhood maltreatment may be related to smaller ACC GM volume; although again it is difficult to dissociate the unique effect of childhood maltreatment from that of co-morbid PTSD, MDD and ASPD and also all the participants in the above-mentioned studies were adults.

3.1.3. Cerebellum

The cerebellum has traditionally been associated with motor control, physical coordination, balance and gait. Accumulating evidence suggests that the cerebellum also plays a role in affective and higher cognitive functions, in particular attention and timing functions (Rubia and Smith, 2004; Schmahmann, 2004; Arnsten and Rubia, 2012). Cerebellar lesions are associated with Cerebellar Cognitive Affective Syndrome, which refers to a constellation of cognitive (decision making, set shifting, working memory), affective (flat affect, depression), behavioural (disinhibition, aggression, obsessive-compulsive behaviours) and linguistic deficits (Schmahmann and Sherman, 1998; Schmahmann et al., 2007). The cerebellum has both structural and functional connections to the PFC, the subcortical limbic structures and monoamine-producing brainstem nuclei and receives input directly and indirectly (via projections from cortical association areas and the midbrain) from nearly all sensory receptors (Schmahmann, 2000). The numerous bidirectional neural connections between the cerebellum and other brain regions including those involved in cognition and emotion processing make it a key region of interest in normal and abnormal brain development. Furthermore, heritable influences on cerebellar volumes are less than for other brain regions thereby suggesting that the development of the cerebellum might be more influenced by environmental factors (Giedd et al., 2007). The cerebellar vermis also has the highest density of glucocorticoid receptors during development, rendering it particularly vulnerable to the effects of early stress (Pavlik and Buresova, 1984).

A few studies documented smaller GM volume in the cerebellum in severely deprived children (Bauer et al., 2009) and children and adolescents with childhood maltreatment-related PTSD (De Bellis and Kuchibhatla, 2006) as well as smaller cerebellum vermis in children with maltreatment-related PTSD (Carrion et al., 2009) compared to healthy controls. However, a couple of studies reported no significant differences in children with maltreatment-related PTSD (Carrion et al., 2001) and in healthy maltreated children (De Brito et al., 2013) compared to healthy controls.

Furthermore, two studies reported direct correlations between brain abnormalities and measures of abuse and/or performance. For instance, children and adolescents with childhood maltreated-related PTSD had smaller total and bilateral cerebellar volumes than non-maltreated patients and healthy controls which did not differ from each other, and this cerebellar reduction was furthermore associated with earlier age of onset and longer duration of childhood maltreatment; thereby suggesting that childhood maltreatment might hinder normal cerebellar development in children and adolescents (De Bellis and Kuchibhatla, 2006). Also, neglected children had smaller bilateral superior-posterior cerebellar lobe volumes compared to healthy controls and the superior-posterior lobe volumes mediated neuropsychological test performance (visual-spatial memory and executive functioning) differences between the two groups, with larger volumes associated with better performance (Bauer et al., 2009).

Therefore, there is some evidence for cerebellum and cerebellar vermis GM volume reduction in children and adolescents who had experienced childhood maltreatment but this is again compounded by comparing PTSD patients exposed to

abuse with healthy controls without controlling for psychiatric comorbidities. Moreover, there are no studies on adults exposed to childhood maltreatment.

3.1.4. Intracranial, Cerebral, Lateral Ventricular and Cortical Cerebrospinal Fluid Volumes

Studies on maltreated children and adolescents with childhood maltreatment-related PTSD have reported smaller intracranial and cerebral volumes and larger right, left and total lateral ventricles and, cortical and prefrontal cortical cerebrospinal fluid (CSF) volumes compared to healthy controls (De Bellis et al., 1999, 2002a; De Bellis and Keshavan, 2003). Intracranial and cerebral volumes each correlated positively with the age of onset of maltreatment and negatively with the duration of the maltreatment experience; while lateral ventricular volumes correlated positively with duration of maltreatment. These robust associations with age of onset and duration of maltreatment suggest that childhood maltreatment may adversely influence normal brain development. Furthermore, maltreated boys with PTSD also showed larger lateral ventricular volumes than male controls and maltreated girls with PTSD; while no lateral ventricular volume differences were seen when maltreated girls were compared with female controls (De Bellis et al., 2002a; De Bellis and Keshavan, 2003). Thus, maltreated boys may be more vulnerable to the effects of severe stress than their female counterparts.

3.1.5. Other Less Commonly Examined Subcortical Brain Structures

Most studies found no significant differences in caudate GM volume in adults (Bremner et al., 1997) and children and adolescents with childhood maltreatment-related

PTSD (De Bellis et al., 1999, 2002a) and in children who had experienced severe early deprivation (Tottenham et al., 2010) compared to healthy controls. However, in a large study of 265 healthy adults with early life stress including childhood maltreatment, participants with greater than two adverse childhood events had smaller caudate nuclei than those without (Cohen et al., 2006). Similarly, studies found no significant differences in putamen GM volume between children and adolescents with childhood maltreatment-related PTSD and healthy controls (De Bellis et al., 1999, 2002a).

Finally, violent adult patients (ASPD and violent schizophrenia) with a history of childhood maltreatment had smaller thalamic volume compared to violent patients without a history of childhood maltreatment and the ASPD patients with a history of childhood maltreatment also had smaller thalamic volume than healthy controls (Kumari et al., 2012). However, adolescent GAD patients exposed to childhood maltreatment had larger left thalamic GM volume than GAD patients without childhood maltreatment as well as healthy controls with and without childhood maltreatment (Liao et al., 2013).

3.2. Childhood Maltreatment and WM Tract Abnormalities

Diffusion-Weighted Imaging (DWI) (Le Bihan et al., 1986) is a non-invasive MRI-based method with high sensitivity to water movements within the architecture of the tissues (Soares et al., 2013). While DWI refers to the contrast of the acquired images, diffusion tensor imaging (DTI) (Basser et al., 1994; Pierpaoli et al., 1996) is a specific type of modelling of the DWI datasets and provides a framework for the analysis and quantification of the diffusion properties of WM. The basic concept behind DTI is that

water molecules diffuse differently along the tissue depending on its type, integrity, architecture and presence of barriers thereby providing information about its orientation and quantitative anisotropy (Chenevert et al., 1990; Beaulieu, 2002). Fractional anisotropy (FA) is the most widely used DTI-based index in brain research which varies in magnitude with the characteristics of the tissue microstructure. For example, FA of the ventricular system is near 0 while FA of the corpus callosum, where fibres are arranged in a regular and parallel fashion, can approach 0.8 to 0.9; and lower than expected FA in a region of fully volumed WM can be an index of compromised WM integrity (Chanraud et al., 2010). Thus, DTI provides a means for vivo exploration of normal WM pathways and enables the identification of alterations present in neurological and psychiatric diseases.

Findings from healthy childhood brain development suggest that WM, which reflects the axonal compartment of myelinated fibres, increases throughout childhood and adolescence (Giedd et al., 1999a; Paus et al., 1999, 2001; Wilke et al., 2007; Tamnes et al., 2010). Using DTI, a more sensitive measure to assess microstructural changes associated with normal brain maturation, substantial increases of FA were seen in the WM tracts within 8-12 years and also between childhood and adulthood (Snook et al., 2005; Peters et al., 2012; Yoshida et al., 2013).

3.2.1. Corpus Callosum Abnormalities in sMRI and DTI Studies

The corpus callosum is the major commissure and the most extensive myelinated fibre tract in the brain that connects and integrates activities between the left and the

right hemisphere. It plays a crucial role in inter-hemispheric communication of sensory, motor and higher cognitive information (Giedd et al., 1996; Gazzaniga, 2000). Nerve fibre connections passing through the corpus callosum are fully formed before birth. Experience-dependent pruning and myelination of fibres through the corpus callosum follows a rostral-caudal pattern that increases callosal size and continues through adolescence (Giedd et al., 1996, 1999b; Thompson et al., 2000). The corpus callosum can be divided into 7 subregions, including (1) rostrum, (2) genu, (3) rostral body, (4) anterior midbody, (5) posterior midbody, (6) isthmus and (7) splenium.

Using sMRI, several studies with the exception of two studies that found no significant differences (Carrion et al., 2009; Mehta et al., 2009a) reported smaller corpus callosum volume in children and adolescents (De Bellis et al., 1999, 2002a; De Bellis and Keshavan, 2003; Teicher et al., 1997, 2004; Jackowski et al., 2008) and female adults (Kitayama et al., 2007) with childhood maltreatment-related PTSD, and in young adults with a history of childhood sexual abuse (Andersen et al., 2008) compared to healthy controls. Corpus callosum volume was also found to be particularly sensitive to the adverse effect of childhood sexual abuse at ages 9-10 years (Andersen et al., 2008).

Furthermore, the rostral-caudal myelination sequence might cause different regions of the corpus callosum to have different windows of vulnerability to early experience (Teicher et al., 2004). De Bellis and colleagues reported greater total corpus callosum area reduction particularly in middle and posterior regions (subregions 4-7) in maltreated children and adolescents with PTSD than in healthy controls (De Bellis et al., 1999, 2002a; De Bellis and Keshavan, 2003). Moreover, maltreated children and

adolescents with PTSD did not show the normal age-related increase in the areas of total corpus callosum and subregion 7 compared to healthy controls, and this finding was more prominent in maltreated boys (De Bellis and Keshavan, 2003). Similarly, the maltreated group had the smallest total corpus callosum area compared with both the psychiatric control and healthy control groups which did not differ significantly from each other, with the most prominent differences between the maltreated group and healthy controls in subregions 4, 5 and 7; thereby suggesting that early traumatic experience rather than psychiatric illness was associated with decreased corpus callosum size (Teicher et al., 2004). Finally, a study of female adults with childhood maltreatment-related PTSD found no significant differences in any of the 7 subregions and total size of the corpus callosum between PTSD patients and healthy controls, but the subregion/total area ratio was significantly smaller in the posterior midbody (subregion 5) of the corpus callosum in the PTSD group compared to healthy controls (Kitayama et al., 2007).

Using DTI to assess possible changes in myelination of WM coherence in the corpus callosum, maltreated children with PTSD had reduced FA in the medial and posterior regions of the corpus callosum compared to healthy controls (Jackowski et al., 2008). Likewise, healthy adolescents exposed to childhood maltreatment had lower FA in the splenium of the corpus callosum than healthy controls (Huang et al., 2012) and this region was also associated with exposure to childhood peer verbal abuse in young healthy adults (Teicher et al., 2010) .

Therefore, these studies suggest that the middle and posterior regions of the corpus callosum may be more affected by exposure to childhood maltreatment although again, most of the studies examined patients with childhood maltreatment-related PTSD without a psychiatric control group. Moreover, the continued development of the PFC into the third decade of life might account for the lack of smaller areas in the anterior part of the corpus callosum (subregions 1, 2 and 3) that map onto the PFC, in maltreated children and adolescents (De Bellis et al., 1999).

3.2.2. Other WM Tract Abnormalities in DTI Studies

Besides the corpus callosum, the integrity of other WM tracts that are compromised in childhood maltreatment include the uncinate fasciculus (Eluvathingal et al., 2006), arcuate fasciculus (Choi et al., 2009), cingulum bundle (Choi et al., 2009; Huang et al., 2012), body of the fornix (Choi et al., 2009), inferior fronto-occipital fasciculus (Huang et al., 2012), as well as the inferior (Choi et al., 2012) and superior longitudinal fasciculus (Huang et al., 2012).

Furthermore, some studies have shown direct correlations between FA values and measures of abuse, psychopathology symptoms and neurocognitive functioning. For instance, children subjected to early severe deprivation had decreased FA in the left uncinate fasciculus (which connects the anterior temporal lobe including the amygdala to the frontal lobe) relative to the right compared to healthy controls who demonstrated relatively equal FA in the two hemispheres. Reduced integrity of this pathway was also associated with difficulties in neurocognitive functioning such as verbal memory and

executive function (Eluvathingal et al., 2006). Young adults exposed to childhood parental verbal abuse, a form of emotional abuse, had reduced FA in: (1) the arcuate fasciculus in the left superior temporal gyrus (which connects the caudal superior temporal with the frontal lobe, and provides a pathway for the PFC to receive and modulate auditory information), (2) the cingulum bundle located in the left fusiform gyrus by the posterior tail of the left hippocampus (which connects the limbic lobe with the neocortex, particularly the cingulate gyrus) and (3) the left body of the fornix compared to healthy controls. Decreased FA in these regions were significantly associated with reduced verbal IQ score, increased ratings of depression and dissociation, and increased ratings of anxiety and somatization, respectively (Choi et al., 2009). Additionally, young adults who witnessed domestic violence during childhood had reduced FA values in the inferior longitudinal fasciculus of left lateral occipital lobe compared to healthy controls, and the degree of FA reduction was associated with the duration of witnessing interparental verbal aggression and with exposure between ages 7 and 13 years. FA values also correlated with ratings of anger-hostility, 'limbic irritability', depression, anxiety, dissociation, somatization as well as neuropsychological measures of visual processing speed (Choi et al., 2012). Finally, healthy adolescents exposed to childhood maltreatment had lower FA values in the left and right superior longitudinal fasciculi, right cingulum bundle projecting to the hippocampus and in the left inferior fronto-occipital fasciculus compared to healthy controls (Huang et al., 2012). FA value in the right superior longitudinal fasciculi correlated positively with psychosocial functioning and negatively with depressive scores. Furthermore, the observed lower FA values in the right and left superior longitudinal fasciculi and right cingulum-hippocampal projection in the maltreated

group at baseline were associated with increased vulnerability to unipolar depression and/or substance abuse at follow-up.

In summary, these studies show that the integrity of the WM tracts that form pathways between structures that have been implicated in sMRI studies of childhood maltreatment especially the frontal-temporo-limbic regions may also be compromised suggesting that structural abnormalities affect the communication between brain regions in addition to isolated brain areas. DTI studies have shown that these frontal-temporo-limbic and frontal-temporal WM tracts that mediate affect control and complex cognitive functions such as executive functioning and attention, respectively, are late developing (Lebel et al., 2008; 2012). Thus, the association between childhood maltreatment and abnormalities in these pathways suggests an environmentally triggered disturbance in normal development of these networks that may underlie the cognitive and emotional problems that develop as a consequence of early adversities such as childhood maltreatment.

3.3. Conclusions

In conclusion, a review of the ROI literature on childhood maltreatment and brain structural abnormalities show that the brain regions that are most consistently affected by childhood maltreatment are the PFC, hippocampus, amygdala, ACC, cerebellum and corpus callosum; suggesting that fronto-limbic networks may be most compromised in childhood maltreatment. However, it is worth noting that the majority of these ROI studies reviewed have tested predominantly for frontal and limbic

abnormalities (Bremner et al., 1997, 2003; Stein et al., 1997; Teicher et al., 1997, 2004, 2012; De Bellis et al., 1999, 2001, 2002a; Driessen et al., 2000; Carrion et al., 2001, 2007, 2009; Vythilingham et al., 2002; De Bellis and Keshavan, 2003; Schmahl et al., 2003; Pederson et al., 2004; Cohen et al., 2006; Kitayama et al., 2006, 2007; Richert et al., 2006; Tupler and De Bellis, 2006; Vermetten et al., 2006; Andersen et al., 2008; Weniger et al., 2008; Mehta et al., 2009a; Tottenham et al., 2010; Morandotti et al., 2013; Samplin et al., 2013; Whittle et al., 2013). A few studies examined the fronto-striatal system and found no effect of childhood maltreatment on the basal ganglia (Bremner et al., 1997; De Bellis et al., 1999, 2002a; Tottenham et al., 2010), but one study found that healthy adults with early life stress including childhood maltreatment had smaller caudate nuclei than those without (Cohen et al., 2006).

Despite the vast number of studies on structural abnormalities in individuals exposed to childhood maltreatment, the findings are not yet conclusive as most studies are confounded by the comorbid psychiatric disorders such as PTSD, MDD, GAD, BPD, ADHD and phobias in the maltreated individuals (please see Table 3.1); thereby making it unclear whether the volumetric abnormalities observed in the maltreated individuals are due to their comorbid psychiatric disorders, histories of childhood maltreatment or due to an interaction between the two. A few studies attempted to isolate the confounding effect of psychiatric comorbidities by either including another group of psychiatric controls without a history of childhood maltreatment (Vythilingham et al., 2002; Teicher et al., 2004; De Bellis and Kuchibhatla, 2006; Morandotti et al., 2013) or another group of participants exposed to childhood maltreatment but without PTSD (Bremner et al., 2003; Pederson et al., 2004). Two studies reported no significant group

differences in the temporal (Vythilingham et al., 2002) and hippocampal (Pederson et al., 2004) GM volumes while the others found GM reduction in the PFC (Morandotti et al., 2013), hippocampal (Vythilingham et al., 2002; Bremner et al., 2003) and cerebellar (De Bellis and Kuchibhatla, 2006) areas as well as reduced corpus callosum (Teicher et al., 2004) in maltreated participants with psychiatric comorbidities compared to non-maltreated psychiatric controls or maltreated participants without PTSD. However, three of them are limited by their relatively smaller sample sizes (Vythilingham et al., 2002; Bremner et al., 2003; De Bellis and Kuchibhatla, 2006). Also, 78% of the participants in the study of Morandotti et al (2013) were on antidepressants and antipsychotics and the other two studies (Pederson et al., 2004; Teicher et al., 2004) did not report whether the participants were taking psychoactive medications. In fact, taking psychoactive medications is another limitation of a few of these structural studies reviewed (please see Table 3.1; Stein et al., 1997; Driessen et al., 2000; Schmahl et al., 2003; Vermetten et al., 2006; Weniger et al., 2008) as these medications such as antidepressants, antipsychotics, benzodiazepine, or psychostimulants, are known to affect brain structure and function (Murphy, 2010; Nakao et al., 2011) thereby making it difficult to determine whether the reported brain abnormalities are associated with childhood maltreatment or confounded by long-term medication effects. Furthermore, some of the studies also did not control for drug abuse (please see Tables 3.1& 3.2) even though drug abuse has been shown to affect brain structure and function (Goldstein and Volkow, 2011).

One way to address direct associations is via correlation analyses between brain changes and abuse measures. Thus, some studies reported significant correlations between brain volumetric abnormalities and abuse severity, age of onset, frequency

and/or duration of childhood maltreatment, in the PFC (Sheffield et al., 2013; van Harmelen et al., 2010), ACC (Treadway et al., 2009; Thomaes et al., 2010), hippocampus (Bremner et al., 1997; Dannlowski et al., 2012a; Teicher et al., 2012; Samplin et al., 2013; Whittle et al., 2013), amygdala (Mehta et al., 2009a; Tottenham et al., 2010; Whittle et al., 2013) and cerebellum (De Bellis and Kuchibhatla, 2006; Bauer et al., 2009) further strengthening the association between childhood maltreatment and the brain regional abnormalities observed.

Therefore, looking at studies with reasonable sample sizes that have controlled for psychiatric comorbidities, medications and drug abuse as well as those that have reported correlations of their findings with childhood maltreatment, brain regions commonly reported to be affected in the maltreated individuals include the PFC (DLPFC, OFC, MPFC), hippocampus, amygdala, ACC and cerebellum. The DLPFC is involved in executive functions such as performance monitoring and manipulation of information in working memory, planning, cognitive flexibility, response inhibition, attention and temporal structuring of goal-directed behaviour (Petrides, 2005). The MPFC, which has extensive connections with subcortical structures (amygdala, nucleus accumbens and hypothalamus) and is part of the paralimbic system that regulates motivation and affect (Compton, 2003), is involved in emotion regulation and social cognition which includes self-knowledge, person perception and mentalizing (Amodio and Frith, 2006). Hence, deficits associated with childhood maltreatment in the DLPFC may underlie the observed problems with inhibitory control, attention and working memory (Chapter 2); while deficits in the MPFC may underlie reported difficulties with emotion processing (Chapter 2). The OFC also receives strong input from the amygdala

and other parts of the limbic system and plays a role in regulating motivated responses (Rempel-Clower, 2007). The ACC receives substantial input from the amygdala and controls the relationship between the emotional limbic system and the autonomic portions of the nervous system, and is involved in the appreciation and expression of emotions and storage of emotional memories (Vogt, 2005). Thus, structural deficits in the OFC and ACC together with deficits in the interconnected limbic areas such as amygdala and hippocampus may be associated with problems in emotion and motivation control, emotion processing and (emotional) memories. Accumulating evidence suggests that besides motor control, the cerebellum also plays a role in affective and higher cognitive functions, in particular attention and timing functions (Rubia and Smith, 2004; Schmahmann, 2004; Arnsten and Rubia, 2012). Hence, alterations in the cerebellum due to childhood maltreatment may also manifest as impairments in attention and reward processing (Guyer et al., 2006; Weller and Fisher, 2012). Therefore, the findings suggest that childhood maltreatment may be associated with abnormalities in the fronto-limbic and fronto-cerebellar networks that mediate emotion and motivation processing as well as executive functions such as response inhibition, attention and working memory, respectively.

Several studies have included participants with various forms of childhood maltreatment such as sexual, physical and emotional abuse, emotional and physical neglect, verbal abuse, early deprivation and witnessing domestic violence (please see Tables 3.1 & 3.2). Given that different types of childhood maltreatment differ in their clinical presentation; for instance, self-harm and eating disorders are more common in females who had been sexually abused (Weierich and Nock, 2008), it is conceivable that

different types of maltreatment may also have different neurobiological, psychiatric and behavioural effects on the individual. For instance, childhood sexual abuse has different effects on brain structure (Heim et al., 2013) and has different psychiatric and behavioural consequences (Ackerman et al., 1998). Thus, it is crucial to examine the effects of various types of childhood maltreatment separately. However, it may be unrealistic to separate physical abuse from typically co-occurring emotional abuse and neglect (Edwards et al., 2003) as it is unlikely for the individual to experience (severe) physical abuse without experiencing at least moderate levels of emotional abuse and neglect concurrently; on the other hand, physical abuse does not always co-occur with sexual abuse. Moreover, using child protective services case records abstraction (physical, sexual, emotional abuse and neglect), latent class analysis revealed four distinctive profiles of childhood maltreatment experiences in which physical abuse was clustered with 1) neglect, 2) emotional abuse, 3) both neglect and emotional abuse and 4) neglect, emotional abuse and sexual abuse (Trickett et al., 2011).

Likewise, the DTI studies on childhood maltreatment included different sample characteristics such as types of childhood maltreatment, presence of comorbid psychiatric disorders and also all except the study of Choi et al (2012) had relatively small sample sizes (<20 participants per group). Hence, more studies are still needed to investigate the effect of childhood maltreatment on the integrity of the WM tracts. Nonetheless, the reduced FA in the frontal-temporo-limbic and frontal-temporal WM tracts observed form pathways between structures that have also been implicated in the sMRI studies in maltreated individuals, suggesting that the structural abnormalities affect the communication between brain regions as well.

Finally, many sMRI studies especially the earlier ones have explored GM differences in childhood maltreatment using ROI-based methods while more recent studies have employed whole-brain methods such as the voxel-based morphometry (VBM; Ashburner and Friston, 2000), a fully automated voxel-by-voxel whole-brain MRI measurement technique (please see Table 3.1). The ROI method has many strengths, namely anatomical validity. However, it also has limitations, including the time-consuming nature of manual ROI drawings in delineating a priori-defined regions and it requires substantial training to ensure rater reliability which makes it difficult to compare many brain regions or large subject groups (Kubicki et al., 2002). Hence, a priori hypotheses are needed to reduce the number of such pre-selected target regions which may provide a biased and inappropriately constrained characterization of anatomy (Friston et al., 2006). In contrast, by surveying the whole brain rather than limiting the search towards a priori hypothesized regions, VBM provides a non-biased measure of highly localized regions that may not be investigated in ROI-based studies and hence extends ROI findings by increasing the anatomical range of volumetric comparisons (Giuliani et al., 2005). Furthermore, systematic studies comparing automated VBM with ROI-based methods have found VBM to be equally specific in detecting local volumetric alternations in expected regions and also capable of detecting remote volume loss in Huntington disease (Douaud et al., 2006; Focke et al., 2014).

Hence, in recent years, more sMRI studies in childhood maltreatment are using the whole-brain based analysis (WBA) (please see Table 3.1). These WBA studies have generally reported GM volume deficits in similar areas as those identified by ROI

studies such as the PFC (DLPFC, OFC, MPFC), temporal lobes and ACC, as well as other areas that are not commonly examined in ROI studies such as the thalamus, insula, parietal and occipital cortices (Tomoda et al. 2009a; Hanson et al. 2010; Edmiston et al. 2011; Dannlowski et al. 2012a; Kumari et al., 2012; Tomoda et al. 2012; De Brito, et al. 2013; Van Dam et al., 2014). A few WBA studies have also reported GM volume enlargement in some areas identified by ROI studies such as the PFC and superior temporal gyrus as well as areas that are not commonly examined in ROI studies such as the occipital cortex and parahippocampal gyri (Carrion, et al., 2009; Hanson, et al., 2010). In addition, similar to ROI studies that found no basal ganglia deficits except for one study by Cohen et al (2006), only two WBA studies reported basal ganglia deficits in healthy individuals with a history of childhood maltreatment (Edmiston, et al., 2011; Dannlowski et al., 2012a). Please refer to Chapter 6 for a meta-analysis of published whole-brain VBM studies of structural abnormalities in childhood maltreatment to elucidate the most robust volumetric GM abnormalities relative to controls to date.

TABLE 3.1. Summary of the Characteristics of Structural MRI Studies in Childhood Maltreatment

Article	N (M/HC)	Gender (M/F)	Children/ Adolescent/ Adult	Childhood Maltreatment Type	Comorbidities (maltreated group)	Medication (maltreated group)	ROI/ WBA	Drug Abuse
Bremner et al. (1997)	17/17	24/10	Adult	PA, SA	PTSD (100%); MDD (86%); BD (14%); SoP (29%); PD (36%); GAD (7%); ED (14%)	NR	ROI	0
Stein et al. (1997)	21/21	0/42	Adult	SA	PTSD (71%); DiD (71%); MDD (29%); SoP (5%); OCD (5%)	14% (amitriptyline, haloperidol, trazadone, alprazolam)	ROI	0
Teicher et al. (1997)	51	26/25	Children	PA, SA, N, VA, WDV	NR	NR	ROI	NR
De Bellis et al. (1999)	44/61	61/44	Children/ Adolescent	PA, SA, EA/WDV	PTSD (100%); MDD (45%); Dysthymia (66%); ODD (52%); ADHD (32%)	14% (stimulants, antidepressants, clonidine)	ROI	14% (cannabis, glue)
Driessen et al. (2000)	21/21	0/42	Adult	PA/EA, SA, EN, PN	BPD (100%); PTSD (57%)	43% (but stopped 1 week prior)	ROI	Drug free \geq 7 days before study

Carrion et al. (2001)	24/24	28/20	Children	PA, SA, EA, PN, WDV	PTSD (50%); Subthreshold PTSD (50%); MDD (13%); DDNOS (4%); SoP (13%); ADHD (13%); SAD (8%); GAD (8%); Simple phobia (8%)	NR	ROI	0
De Bellis et al. (2001)	9/9	10/8	Children	SA	PTSD (100%); MDD (89%); ODD (56%); ADHD (33%); SAD (11%)	0 (before baseline scan); 78% (antidepressant/ antianxiety after baseline scan)	ROI	0
De Bellis et al. (2002a)	28/66	45/49	Children/ Adolescent	PA, SA, EA, N WDV	PTSD (100%); MDD (50%); Dysthymia (75%); ODD (25%); ADHD (29%); SAD (21%)	0	ROI	0
De Bellis et al. (2002b)	43/61	61/43	Children/ Adolescent	PA, SA, EA, N, WDV	PTSD (100%)	0	ROI	NR
Vythilingham et al. (2002)	21/14 (& 11 MDD only)	0/46	Adult	PA, SA	MDD (100%); Dysthymia (10%); PTSD (66%); PD (20%); GAD (10%); OCD (10%); SD	0	ROI	15% (cannabis, cocaine)

					(5%); ED (14%); SP (5%)			
Bremner et al. (2003)	22^/11 ^(CM with PTSD:10, CM w/o PTSD:12)	0/33	Adult	SA	PTSD (45%); MDD (9%); PD (14%)	Free of all mediations \geq 4 weeks prior	ROI	9% (cocaine, marijuana)
De Bellis & Keshavan (2003)	61/122	93/90	Children/ Adolescent	PA (51%), SA (80%), EA/WDV (72%),	PTSD (100%); MDD (51%); Dysthymia (67%); ODD (43%); ADHD (34%); SAD (10%)	0	ROI	0
Schmahl et al. (2003)	10/23* (10 out of 23 non-CM controls had a trauma history)	0/33	Adult	PA, SA	BPD (100%); PTSD (30%); Depression (40%); PD (40%); ED (30%)	90%	ROI	24% (cannabis, cocaine, opioid, polysubstance, stimulant)
Pederson et al. (2004)	34^/17 ^(CM with PTSD:17, CM w/o PTSD:17)	0/51	Adult	PA, SA, EA	PTSD (50%); other Axis 1 psychiatric disorders NR	NR	ROI	NR
Teicher et al. (2004)	28/115 (& 23 psychiatric controls)	96/70	Children/ Adolescent	PA, SA, EA, N WDV	PTSD (50%); Mood disorders & suicidal ideation or self-	NR	ROI	NR

					destructive behaviour (71%); DBD (14%)			
Cohen et al. (2006)	265	133/132	Adult	Adverse childhood events including PA, SA, EA, N, WDV	0	0	ROI	0
De Bellis & Kuchibhatla (2006)	58/98 (& 13 GAD only)	88/81	Children/ Adolescent	SA, WDV	PTSD (100%); Dysthymia (60%); MDD (52%); ODD (43%); ADHD (34%); SAD (5%)	0	ROI	0
Kitayama et al. (2006)	8/13	2/19	Adult	NR	PTSD (100%); PD (25%)	NR	ROI	NR
Richert et al. (2006)	23/24	27/20	Children	PA, SA, EA, PN, WDV	PTSS (100%); MDD (13%); DDNOS (4%); SoP (13%); ADHD (13%); SAD (9%); Simple phobia (9%)	0	ROI	0

Tupler & De Bellis (2006)	61/122	93/90	Children/ Adolescent	PA, SA, EA, N, WDV	PTSD (100%); 87% had comorbid psychiatric disorders but disorder types NR	0	ROI	0
Vermetten et al. (2006)	15/23	0/38	Adult	PA, SA	DiD (100%); PTSD (100%); MDD (93%); SD (7%)	100% (antidepressants, antipsychotics, benzodiazepines, anxiolytics, estrogens, opiate antagonists, psychostimulants)	ROI	40%
Carrion et al. (2007)	15/0	6/9	Children	PA, SA, EA, PN, WDV	PTSD (100%); other psychiatric disorders NR	NR	ROI	0
Kitayama et al. (2007)	9/9	0/18	Adult	PA, SA, WDV	PTSD (100%); PD (22%)	NR	ROI	33%
Andersen et al. (2008)	26/17	0/43	Adult	SA	PTSD (15%); MDD (12%); DDNOS (4%); OCD (4%); ADHD (4%); GAD	0	ROI	0

					(4%); SP (4%); ED (4%)			
Weniger et al. (2008)	23^/25 ^(CM with PTSD: 10; CM with DA/DiD: 13)	0/48	Adult	PA, SA, N	BPD (100%); MDD (87%); PTSD (43%); DA/DiD (57%); ED (9%)	65% (fluoxetine, doxepine, mirtazapine, trimipramine, amitriptyline, diazepam, lorazepam)	ROI	0
Bauer et al. (2009)	31/30	31/30	Children	Severe early deprivation/ N	NR	NR	ROI	NR
Carrion et al. (2009)	24/24	28/20	Children	PA, SA, EA, PN, WDV	PTSD (50%); Subthreshold PTSD (50%); MDD (13%); DDNOS (4%); SoP (13%); ADHD (13%); SAD (8%); GAD (8%); Simple phobia (8%)	21% (stimulants and/or SSRIs)	ROI/ WBA	0
Mehta et al. (2009a)	14/11	12/13	Adolescents	Severe early deprivation/ N	NR	NR	ROI	NR

Tomoda et al. (2009a)	23/14	0/37	Adult	SA	PTSD (17%); MDD (17%); Depersonalization disorder (4%)	0	WBA	0
Tomoda et al. (2009b)	23/22	21/24	Adult	HPCP	ADHD (4%)	0	WBA	0
Treadway et al. (2009)	19 MDD^/19 ^ (correlation analysis with abuse status within MDD group only)	18/20	Adult	PA, SA, EA, EN, PN	MDD (100%); AD (37%)	Antidepressant- free at time of scanning	ROI/ WBA	0
Frodl et al. (2010)	43 MDD/44 (interaction analysis b/w diagnosis & abuse status)	37/50	Adult	EN, PN	MDD (100%)	21% (SSRI), 26% (tricyclic antidepressants), 14% (mirtazapine), 12% (venlafaxine), 9% (reboxetine), 5% (maprotiline)	ROI/ WBA	0
Hanson et al.	31/41*	45/27	Children	PA	CD (6%); ED (6%);	NR	WBA	NR

(2010)					MDD (3%)		(TBM)	
Landre et al. (2010)	17/17	0/34	Adults	SA	PTSD (100%); MDD (47%); suicide risk (65%); Agoraphobia (19%); Addiction (6%)	0	WBA	0
Thomaes et al. (2010)	31/30	0/61	Adult	PA, SA	PTSD (100%); AD (70%); MDD (64%); ED (8%); Other mood disorder (9%); BPD (33%); Cluster C personality disorder (30%)	64% (fluoxetine), 48% (benzodiazepines)	ROI/ WBA	0
Tottenham et al. (2010)	34/28*	13/49	Children	Severe early deprivation/ N	53% had >1 psychiatric disorder; AD (18%)	NR	ROI	NR
Van Harmelen et al. (2010)	84^/97* ^(12 HCs in CM group, 40 HCs in non-CM group)	61/120	Adult	PA, SA, EA	MDD (77%); AD (68%)	0	ROI/ WBA	0
Edmiston et al.	42	21/21	Adolescent	PA, SA, EA,	0	0	WBA	NR

(2011)				EN, PN				
Tomoda et al. (2011)	21/19	16/24	Adult	PVA	Mood disorders (48%); AD (24%)	0	WBA	0
Carballedo et al. (2012)	8/32 20 with family history of MDD (FHP): 4 EA, 16 non-EA 20 without family history of MDD (FHN): 4 EA, 16 non-EA	14/26	Adult	EA	0	0	ROI/ WBA	0
Dannlowski et al. (2012a)	145	75/70	Adult	PA, SA, EA, EN, PN	0	0	ROI/ WBA	NR
Kumari et al. (2012)	17/15 (& 9 violent not deprived patients)	41/0	Adult	Psychosocial deprivation including PA, SA	ASPD (59%); VSZ (41%)	NR	ROI/ WBA	0
Teicher et al. (2012)	193	73/120	Adult	PA, SA,WDV, HPCP, (P)VA	MDD (25%); PTSD (7%); AD (21%); PD (2%); ADHD (3%);	0	ROI	0

					ED (2%); BD (2%)			
Tomoda et al. (2012)	22/30	14/38	Adult	WDV	MDD (41%); AD (32%); PTSD (18%); Personality disorders (5%); ED (9%)	0	WBA	0
Chaney et al. (2013)	30 [^] /53* ^(10 HCs in CM group, 36 HCs in non-CM group)	34/49	Adult	PA, SA, EA, EN, PN	MDD (67%)	32% (SSRIs), 32% (venlafaxine, mirtazapine)	ROI/ WBA	0
De Brito et al. (2013)	18/20	21/17	Children	PA, SA, EA, N	Participants reported no psychiatric diagnoses and were matched on anxiety, depression and PTSD symptoms	0	ROI/ WBA	0
Liao et al. (2013)	26 [^] /25* ^(12 HCs in CM group, 13 HCs in non-CM group)	26/25	Adolescent	PA, SA, EA, EN, PN	GAD (54%)	0	ROI/ WBA	0
Lu et al.	24/24	18/30	Adult	PA, SA, EA,	0	0	WBA	0

(2013)				EN, PN				
Morandotti et al. (2013)	11/19 (& 7 BPD only)	11/26	Adult	PA, SA	BPD (100%); MDD (56%); Dysthymia (22%); PD (6%)	78% (antidepressants, mood stabilizers, antipsychotics)	ROI	0 (within the 6 months prior to the study)
Samplin et al. (2013)	67	30/37	Adult	PA, SA, EA, EN, PN	0	0	ROI	0
Sheffield et al. (2013)	24/26 (& 23 psychosis only)	32/41	Adult	SA	Psychosis (100%); AD (46%); PTSD (29%); OCD (17%); PD (8%); ED (8%); GAD (4%)	93% (chlorpromazine)	ROI/WBA	0
Whittle et al. (2013)	117	60/57	Adolescent	PA, SA, EA, EN, PN	AD (13%); externalizing disorder (5%) before baseline	NR	ROI	0
Kumari et al. (2014)	18/15 (& 9 violent not deprived patients)	42/0	Adult	Psychosocial deprivation including PA, SA	ASPD (61%); VSZ (39%)	NR	ROI	0

VanDam et al. (2014)	69 [^] /108* ^(25 HCs in CM group, 73 HCs in non-CM group)	113/64	Adult	PA, SA, EA, EN, PN	SUD (64%); MDD (20%); PTSD (23%); AD (12%)	0	WBA	Abstinent for 4-5weeks
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Abbreviations: N (CM/HC): Sample size (Childhood maltreatment group/Healthy control group); *: non-maltreatment (but not healthy) control group; M/F: Male/Female; ROI/WBA: Region-of-Interest/Whole-Brain Analysis; PA: Physical abuse; SA: Sexual abuse; EA: Emotional abuse; EN: Emotional neglect; PN: Physical neglect; WDV: Witnessing domestic violence; N: Neglect; (P)VA: (Parental) Verbal abuse; NR: Not reported; MDD: Major depressive disorder; PD: Panic disorder; OCD: Obsessive compulsive disorder; ODD: Oppositional defiant disorder; CD: Conduct disorder; GAD: Generalized anxiety disorder; ADHD: Attention deficit hyperactivity disorder; SP: Specific phobia; PTSD: Post-traumatic stress disorder; SAD: Separation anxiety disorder; SoP: Social phobia; DDNOS: Depressive disorder not otherwise specified; AD: Anxiety disorder; BD: Bipolar disorder; BPD: Borderline personality disorder; LD: Learning disorders; MPD: Multisomatoform pain disorder; DD: Depressive disorders; DiD: Dissociative disorders; SD: Somatoform disorders; ED: Eating disorders; MVA: Motor vehicle accident; DBD: disruptive behavioural disorders; PTSS: post-traumatic stress symptoms; DA: Dissociative amnesia; HPCP: Harsh parental corporal punishment; TBM: Tensor-based morphometry; ASPD: Antisocial personality disorder; VSZ: violent schizophrenia; SUD: Substance use disorders.

TABLE 3.2. Summary of the Characteristics of DTI Studies in Childhood Maltreatment

Article	N (M/HC)	Gender (M/F)	Children/ Adolescent/ Adult	Childhood Maltreatment Type	Comorbidities (maltreated group)	Medication (maltreated group)	ROI/ WBA (TBSS)	Drug Abuse
Eluvathingal et al. (2006)	7/7	5/9	Children	Severe early deprivation	0	No psychoactive medications within the past 4 weeks	ROI	0
Jackowski et al. (2008)	17/15	14/20	Children	PA, SA, EA, N, WDV	PTSD (100%); MDD (41%); Other depressive diagnoses (30%); ODD (12%); ADHD (6%)	0	ROI	NR
Choi et al. (2009)	16/16	9/23	Adult	Parental VA	GAD (13%); PD (6%); OCD (6%); ADHD (6%)	0	WBA (TBSS)	0
Teicher et al. (2010)	63	23/40	Adult	Peer VA	0	0	WBA (TBSS)	NR
Choi et al. (2012)	20/27	12/35	Adult	WDV	MDD (20%); PTSD (10%); GAD (10%); SoP (10%); ADHD (5%)	NR	WBA (TBSS)	0

Huang et al. (2012)	19/13	11/21	Adolescent	PA, SA, EA, PN, WDV	0	0	WBA (TBSS)	0
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Abbreviations: N (M/HC): Sample size (Maltreatment group/Healthy control group); M/F: Male/Female; ROI/WBA: Region-of-Interest/Whole-Brain Analysis; TBSS: Tract-Based Spatial Statistics; PA: Physical abuse; SA: Sexual abuse; EA: Emotional abuse; EN: Emotional neglect; PN: Physical neglect; WDV: Witnessing domestic violence; N: Neglect; VA: Verbal abuse; NR: Not reported; MDD: Major depressive disorder; PD: Panic disorder; OCD: Obsessive compulsive disorder; ODD: Oppositional defiant disorder; GAD: Generalized anxiety disorder; ADHD: Attention deficit hyperactivity disorder; PTSD: Post-traumatic stress disorder; SoP: Social phobia.

CHAPTER 4

Brain Functional Abnormalities in Childhood Maltreatment (fMRI Studies)

In contrast to the vast number of studies on structural brain abnormalities associated with childhood maltreatment, relatively fewer functional magnetic resonance imaging (fMRI) studies have been published in individuals with a history childhood maltreatment using task-based and resting-state fMRI (please see Table 4).

4.1. Task-Based fMRI Studies

4.1.1. Memory (Non-Traumatic Materials)

In the first ROI fMRI study using a visual/verbal working memory task in four groups of male participants (healthy controls, severe childhood physical abuse only, serious violent offenders only, serious violent offenders with severe childhood physical abuse), violent offenders who had suffered severe childhood physical abuse showed reduced right hemisphere functioning, particularly in the right temporal cortex, compared to the other three groups; while the abuse only group showed relatively lower left, but higher right, activation of the superior temporal gyrus compared to the other three groups and they also performed significantly poorer on the task than the other three groups. Childhood physical abuse was associated with reduced functioning in all lobes in the left hemisphere but only the frontal and temporal lobes in the right hemisphere. Hence, comparatively good right temporal functioning might protect individuals predisposed to violence (by virtue of being abused during childhood) from perpetrating serious violence later in adulthood (Raine et al., 2001).

4.1.2. Inhibitory Control

Two whole-brain based analysis (WBA) studies investigated response inhibition in adolescents exposed to childhood maltreatment using the go/no-go task (Carrion et al., 2008) and the stop-change task (a variant of the stop task) (Mueller et al., 2010). During successful inhibition, adolescents with post-traumatic stress symptoms (PTSS) secondary to childhood maltreatment had decreased activation in the left DLPFC but increased activation in the bilateral medial frontal/ACC relative to healthy controls. Behaviourally, there were no significant group differences in percent correct or reaction time for the go trials, no-go trials or all trials combined (Carrion et al., 2008). Adopted adolescents with early-life stress (caregiver deprivation), however, showed prolonged reaction times to switch from a prepotent response (“go”) to an alternative response (“change”) than healthy controls and exhibited greater activation in the left IFC, ACC, striatum, insula, right dorsal ACC and bilateral pre-and postcentral gyri compared to healthy controls (Mueller et al., 2010).

However, in a recent whole-brain functional connectivity study of inhibitory control networks in healthy adults with a history of childhood maltreatment using the stop task, maltreatment was not associated with changes in brain activation and task performance but was associated with decreased functional connectivity of the IFC and dorsal ACC which was related to symptoms of impulsivity and inattention (Elton et al., 2013). In particular, females with higher exposure to childhood maltreatment and more negative left IFC-dorsal ACC connectivity exhibited better inhibitory control and lesser symptoms of impulsivity and inattention; whereas a more negative coupling of the left

IFC-dorsal ACC path was not adaptive for males. On the other hand, less inhibitory influence of the dorsal ACC on the right IFC in males with more exposure to childhood maltreatment was associated with better inhibitory control; while greater inhibitory influence of the dorsal ACC on the right IFC in males with less exposure to childhood maltreatment was associated with better inhibitory control.

Therefore, these studies suggest that childhood maltreatment is associated with abnormal activation in the ACC and PFC regions in adolescents but not in adults, as well as decreased functional connectivity between these regions in adults during response inhibition. However, more WBA studies are still needed to examine the integrity of the inhibitory networks in adolescents and adults with a history of childhood maltreatment.

4.1.3. Emotion Processing

Most of the fMRI studies on childhood maltreatment examined emotion processing in children and adolescents (Maheu et al., 2010; McCrory et al., 2011, 2013; Tottenham et al., 2011; De Bellis et al., 2012; Garrett et al., 2012; Liu et al., 2012; Goff et al., 2013) and adults (Taylor et al., 2006; Grant et al., 2011; Dannlowski et al., 2012a, 2012b; Edmiston and Blackford, 2013; Fonzo et al., 2013; van Harmelen et al., 2013) with a history of childhood maltreatment. Some of the studies are ROI (Taylor et al., 2006; Maheu et al., 2010; McCrory et al., 2011; De Bellis et al., 2012; Goff et al., 2013) while most of them are WBA (Grant et al., 2011; Tottenham et al., 2011; Dannlowski et al., 2012a, 2012b; Garrett et al., 2012; Liu et al., 2012; Edmiston and Blackford, 2013; Fonzo et al., 2013; McCrory et al., 2013; van Harmelen et al., 2013) studies.

Early Caregiver Deprivation

Three studies investigated the effects of early caregiver deprivation on neural responses to emotional faces in children (Tottenham et al., 2011) and adolescents (Maheu et al., 2010; Goff et al., 2013) using WBA and ROI approach, respectively.

Relative to healthy controls, deprived individuals exhibited significantly greater activation in the left amygdala (Maheu et al., 2010; Tottenham et al., 2011), right amygdala (Tottenham et al., 2011) and left anterior hippocampus (Maheu et al., 2010) during the presentation of fearful faces and the amygdala activity correlated negatively with social competence and mediated the association between early rearing conditions and the decreased eye-contact observed (Tottenham et al., 2011). Deprived youths also had greater activation than healthy controls in the left amygdala during the processing of angry expressions which was positively associated with the number of placements in foster care and negatively related to the time spent in the adoptive family (Maheu et al., 2010). Finally, deprived adolescents also exhibited significantly lower nucleus accumbens activation relative to healthy controls while viewing happy faces, which was associated with higher levels of depression (Goff et al., 2013).

At the performance level, deprived adolescents had faster reaction times for angry faces than healthy controls (Maheu et al., 2010); while there were no significant group differences in the other two studies (Tottenham et al., 2011; Goff et al., 2013).

Therefore, children and adolescents with early caregiver deprivation and emotional neglect exhibited abnormally enhanced activation in the limbic regions of

amygdala and hippocampus in response to negative facial expressions (angry, fearful) and reduced activation in the nucleus accumbens in response to happy faces which were furthermore associated with longer and poorer institutional care conditions as well as adverse outcomes such as social incompetence and depression. Nonetheless, more WBA studies are still needed to examine the neural correlates of emotion processing especially in adults who had experienced early caregiver deprivation/emotional neglect.

Individuals Exposed to Childhood Maltreatment with Depression/Anxiety Disorders

Three studies examined the neural reactivity to emotional stimuli in adolescents (De Bellis et al., 2012) and adults (Grant et al., 2011; van Harmelen et al., 2013) with depression and/or anxiety disorders and a history of childhood maltreatment. One study examined the neural response to novel vs familiar face stimuli in adults who had experienced childhood maltreatment with an inhibited temperament including depression and anxiety disorders (Edmiston and Blackford, 2013).

In the small pilot ROI study on adolescents with depression and a history of childhood maltreatment (De Bellis et al., 2012), depressed youths exposed to abuse had both significantly decreased activation to attentional targets in cognitive control circuits [left middle frontal and right precentral gyri] and increased activation to sad distractors in ventral emotional circuits [bilateral amygdala, left subgenual anterior cingulate (sgACC), left inferior frontal and right middle temporal gyri] compared to healthy controls. They also had significantly decreased activation to both attentional targets and sad distractors in the left posterior middle frontal gyrus, which had been found to be specifically activated in healthy adolescents compared to adults by both attentional

targets and sad distractors (Wang et al., 2008), relative to healthy controls indicating dysfunction of this region in the process of inhibiting emotional distraction (De Bellis et al., 2012). There were no significant group differences in task performance.

In a WBA study, adults with MDD and a history of childhood maltreatment had greater activation in the right amygdala in response to sad faces compared to MDD only patients and healthy controls; thereby suggesting that heightened amygdala reactivity and sensitivity to aversive stimuli was not characteristic of persons with depression in general but may instead be driven primarily by sensitization of amygdala to persistent exposure to elevated glucocorticoid levels following early life stress (Grant et al., 2011). Furthermore, childhood physical abuse was positively associated with heightened right amygdala response to sad faces. There were no significant group differences in task performance.

In another WBA study, adults with MDD and/or anxiety disorders and healthy controls with reported childhood emotional maltreatment (CEM) showed enhanced bilateral amygdala reactivity to both positive (happy) and negative (angry, fearful, sad) emotions compared to patients and healthy controls reporting no CEM; thereby indicating that individuals with a history of CEM interpreted all facial expressions as highly salient and that the amygdala hyper-reactivity to emotional faces may not be directly linked to the development of psychopathology (van Harmelen et al., 2013).

Finally, using a WBA approach, childhood maltreatment exposure was significantly correlated with greater activation in bilateral fusiform gyri and left

hippocampus during viewing of neutral novel compared to familiar faces indicating a heightened sensitivity to novelty in adults with an inhibited temperament and a history of childhood maltreatment (Edmiston and Blackford, 2013).

Thus, depressed adolescents with a history of abuse demonstrated dysfunction of neural systems related to cognitive control and emotional processing and in particular, the left posterior middle frontal gyrus was dysfunctional during inhibiting emotional (sad) distraction. Additionally, in depressed and/or anxious adults with a history of childhood maltreatment, the amygdala hyper-reactivity to emotional (sad) faces may be more related to the adverse childhood experiences than concurrent psychopathology.

Individuals Exposed to Childhood Maltreatment with Post-Traumatic Stress Disorder/Symptoms

Two WBA studies examined emotion processing in adolescents (Garrett et al., 2012) and adults (Fonzo et al., 2013) with PTSD and a history of childhood maltreatment. Relative to healthy controls, maltreated youths with PTSD symptoms showed significantly greater activation in the amygdala/hippocampus, MPFC and insula while viewing angry faces; greater activation in the amygdala/hippocampus, insula and left VLPFC in response to neutral faces, as well as greater activation in the left VLPFC but decreased activation in the DLPFC in response to happy faces (Garrett et al., 2012).

In female adults with PTSD, childhood maltreatment severity correlated with greater ventral ACC activation and lesser amygdalo-insular functional connectivity during the processing of angry faces. During fear processing, childhood maltreatment

severity correlated with greater connectivity between limbic (insula/amygdala) and prefrontal regions (ACC and dorsal PFC) as well as lesser amygdalo-insular connectivity (Fonzo et al., 2013).

Hence, it seems that angry facial expressions may have particular relevance to PTSD patients who had suffered from childhood maltreatment where the early traumatic experiences and/or current PTSD symptoms (such as hypervigilance) may prime the amygdala to be more sensitive to trauma-related anger stimuli and greater ventral ACC neural resources was thus deployed towards limbic inhibition in response to threat cues; which is also consistent with the greater ventral ACC-amygdalar functional connectivity observed during fear processing.

Individuals Exposed to Childhood Maltreatment without Psychiatric Comorbidities

The majority of the fMRI studies on childhood maltreatment-related functional abnormalities examined maltreated participants with various psychiatric comorbidities (please see Table 4) which makes it difficult to infer if the abnormalities reported are associated with the comorbid psychiatric disorders or if they are the consequences of maltreatment in participants without any history of psychiatric disorders and hence constitute potential vulnerability markers.

Nevertheless, a few studies examined the association between childhood maltreatment and emotion processing in maltreated children with comparable level of psychiatric symptoms as the comparison group (McCrory et al., 2011; 2013), in healthy disadvantaged adolescents (Liu et al., 2012) and healthy adults (Taylor et al., 2006;

Dannlowski et al., 2012a, 2012b) thereby minimising the potential confounding effects of psychiatric comorbidities.

In the ROI (McCrory et al., 2011) and WBA (McCrory et al., 2013) paediatric studies, maltreated children exhibited greater activation in the right amygdala (McCrory et al., 2011; McCrory et al., 2013) and bilateral anterior insula (McCrory et al., 2011) to angry faces along with greater activation in the right amygdala to happy faces (McCrory et al., 2013) compared to non-maltreated children. The degree of activation in the left anterior insula was positively correlated with the severity of violence exposure (McCrory et al., 2011). The level of amygdala response to angry faces was negatively associated with age at onset of emotional maltreatment and neglect, and amygdala activation to angry and happy faces was positively associated with the duration of emotional maltreatment (McCrory et al., 2013).

In another ROI study, healthy adults with childhood family stress including physical abuse (i.e. risky families) had significantly greater activation in the left amygdala in response to negative emotional faces (angry, fearful) than those from non-risky families and showed greater right VLPFC activation correlating with greater amygdala activation suggesting a possible deficit in their emotion regulation abilities to effectively recruit right VLPFC for regulating amygdala responses to negative emotional faces (Taylor et al., 2006).

Using whole-brain regression approach, significant negative correlations were found between cortisol response to a social stressor and fear-related brain activation in

the left hippocampus, inferior parietal lobule and precentral gyrus in healthy disadvantaged adolescents with reported childhood maltreatment (Liu et al., 2012). Finally, childhood maltreatment in healthy adults was strongly correlated with right amygdala responsiveness to fearful/angry (Dannlowski et al., 2012a) and sad (Dannlowski et al., 2012b) faces, where emotional abuse and emotional neglect were the strongest predictors followed by physical abuse, physical neglect and sexual abuse (Dannlowski et al., 2012a, 2012b). Other brain areas with similar positive associations between maltreatment experiences and neural processing of subliminal sad faces included the right anterior insula, left rostral ACC and medial prefrontal areas, which have strong connections to the amygdala and belong to a para-limbic anterior emotion processing system (Phillips et al., 2008) involved in the initial generation and experience of affective states (Dannlowski et al., 2012b).

These important fMRI studies that attempted to control for psychiatric comorbidities in the maltreatment group show that childhood maltreatment in children is associated with abnormally enhanced activation in limbic regions, especially the amygdala and insula during the processing of angry faces and this is related to more severe violence exposure as well as longer duration and earlier age at onset of CEM. However in adults, besides these limbic regions the VMPFC and other para-limbic regions also showed abnormal activation particularly during negative emotion processing (angry, fearful and sad) and the strongest association for the heightened amygdala responsiveness was with CEM.

4.1.4. Reward Processing

Two studies examined reward processing in adolescents (Mehta et al., 2009) and adults (Dillon et al., 2009) with a history of childhood maltreatment using the monetary incentive delay (MID) task. In a WBA study, Romanian adolescents who had experienced severe global deprivation including emotional neglect in early life reported hyporesponsive reward anticipation in the basal ganglia (significant in the ventral striatum, trend in the caudate nucleus) across all reward levels compared to healthy controls despite comparable performance accuracy. Healthy controls showed an increase in activation in these regions depending on the reward level but no such differences were found in the maltreated group (Mehta et al., 2009).

Similarly, in a ROI study in adults exposed to childhood maltreatment, maltreated participants displayed a weaker response to reward cues in the left globus pallidus (trend in the putamen) compared to healthy controls despite comparable performance accuracy. Healthy controls also generated a stronger response to reward cues than to no-incentive or loss cues in the left putamen and globus pallidus but no such differences were found in the maltreated group (Dillon et al., 2009).

Therefore, it seems that childhood maltreatment is associated with reduced activation of the basal ganglia during reward processing. However, more WBA studies are needed to examine other brain regions and networks that may also be compromised during reward processing in individuals exposed to childhood maltreatment.

4.1.5. Sensory Processing

Two WBA studies examined sensory processing in adults who had experienced childhood maltreatment using non-traumatic olfactory stimuli (Croy et al., 2010) and the empathetic-pain-inducing visual paradigm (Noll-Hussong et al., 2010).

Maltreated women showed normal activation in the olfactory projection areas but additionally enhanced activation in multiple, mainly neocortical, areas that are parts of those involved in associative networks including the precentral frontal lobe, inferior and middle frontal structures, posterior parietal lobe, occipital lobe and PCC as well as reduced activation in the hippocampus, OFC, ACC and cerebellum relative to non-maltreated controls; indicating that childhood maltreatment may be associated with an altered processing of olfactory stimuli but not functional olfactory deficits (Croy et al., 2010).

In the other study, adult patients suffering from multisomatoform pain disorder with a history of childhood sexual abuse exhibited increased activation in the left lateral and medial superior frontal gyri and reduced activation in the left hippocampus compared to patients who had not experienced abuse in response to psychological painful stimuli (Noll-Hussong et al., 2010).

4.1.6. Traumatic Material Processing

Two WBA studies compared the neural correlates of traumatic memories in traumatized adults who had developed PTSD as a result of childhood sexual abuse or

motor vehicle accident with traumatized adults who had not developed the full PTSD (i.e. they had sub-threshold PTSD) as a result of childhood sexual abuse or motor vehicle accident using the script-driven symptom provocation paradigm (Lanius et al., 2001, 2003). The full PTSD group showed less activation in the bilateral thalamus, ACC and medial frontal gyri than the sub-threshold PTSD group during the traumatic (Lanius et al., 2001) and emotional (sad, anxious and traumatic) scripts (Lanius et al., 2003).

4.1.7. Social Exclusion

In the only WBA study on the neural responses to social exclusion using the Cyberball task in adult patients reporting CEM (van Harmelen et al., 2014), severity of CEM was positively associated with increased dmPFC activation to social rejection across all participants (i.e. patients with a history of abuse and healthy controls).

4.2. Resting-State Functional Connectivity Studies

Recently, four ROI (Cisler et al., 2013; Herringa et al., 2013; van der Werff et al., 2013a, 2013b) and one WBA (Wang et al., 2013) study examined the resting-state functional connectivity (RSFC) in adolescents (Herringa et al., 2013) and adults (Cisler et al., 2013; van der Werff et al., 2013a, b; Wang et al., 2013) with reported childhood maltreatment.

Childhood maltreatment in adolescents was associated with decreased functional connectivity between the left hippocampus and the vmPFC, specifically the sgACC as well as decreased connectivity between the right amygdala and the sgACC (females

only) within the brain's fear-regulatory circuit which may reduce the capacity of the hippocampus to engage in PFC-mediated recall of fear extinction in the absence of threat and impair the modulation of negatively valenced emotional responses (Herringa et al., 2013). The decreased fronto-hippocampal and-amygdala connectivity was furthermore related to greater internalising symptoms.

In the only whole-brain RSFC study in adults exposed to childhood maltreatment, there was a widespread reduction of functional connectivity in brain regions within the prefrontal-limbic-thalamic-cerebellar circuit especially in the dmPFC, VLPFC and DLPFC in MDD patients with a history of childhood neglect compared to MDD only patients and healthy controls which furthermore correlated significantly with measures of childhood neglect; while both MDD groups showed an overlapping reduction of functional connectivity in the bilateral vmPFC/ventral ACC relative to healthy controls (Wang et al., 2013).

CEM has a profound effect on the RSFC in the limbic and salience networks but not the default-model network (van der Werff et al., 2013a). In particular, the study found that compared to the psychopathology-matched control group, the CEM group had reduced negative connectivity between the right amygdala and the bilateral precuneus possibly reflecting disturbances in emotional and cognitive (self) processing, as well as reduced positive connectivity between the right amygdala and a cluster in the left hemisphere extending from the OFC and insula to the hippocampus and putamen possibly reflecting poor emotion regulation. Within the salience network, the CEM group also had lesser negative connectivity between the left dorsal ACC and the right

angular cortex and precuneus possibly reflecting deficits in relating internal and external stimuli to oneself, as well as reduced positive connectivity between the left dorsal ACC and a bilateral frontal cluster containing the MPFC, paracingulate gyrus and frontal pole possibly reflecting problems with reward-guided learning and decision making (van der Werff et al., 2013a).

Examining RSFC patterns specific for resilience to childhood maltreatment in the salience (van der Werff et al., 2013b) and emotion regulation (Cisler et al., 2013) networks, resilient adults had greater negative connectivity between the left dorsal ACC and the bilateral lingual and occipital fusiform gyri which might reflect an increased ability to encode harmful experiences in verbal declarative memory (van der Werff et al., 2013b), as well as decreased integration of the bilateral VLPFC, dorsal ACC and left DLPFC and amygdala into the emotional regulation network (Cisler et al., 2013) compared to non-resilient and healthy controls.

Therefore, these RSFC studies show that childhood maltreatment in adolescents is associated with reduced fronto-limbic functional connectivity within the fear-regulatory circuit which was furthermore related to greater internalising symptoms. In adults, exposure to childhood maltreatment is associated with widespread reduction of functional connectivity within the prefrontal-limbic-thalamic-cerebellar circuit particularly the salience and limbic emotional regulation networks that are involved in (emotional) stimulus processing, emotion regulation, decision making and self-referential processing. Nonetheless, more whole-brain RSFC studies are needed to

examine the functional connectivity and integrity of brain networks especially in young people with a history of childhood maltreatment.

4.3. Conclusions

In summary, most of the fMRI studies on childhood maltreatment used WBA while 11 studies used ROI (please see Table 4; Raine et al., 2001; Taylor et al., 2006; Dillon et al., 2009; Maheu et al., 2010; McCrory et al., 2011; De Bellis et al., 2012; Goff et al., 2013; Cisler et al., 2013; Herringa et al., 2013; Van der Werff et al., 2013a, b) analysis. So far, studies of individuals exposed to childhood maltreatment have consistently identified altered activations of prefrontal regions. For instance, studies on executive functions such as working memory (Raine et al., 2001) and inhibitory control (Carrion et al., 2008; Mueller et al., 2010; Elton et al., 2013) reported altered activations of DLPFC, IFC and medial frontal cortex; while studies of non-executive functions such as emotion (Taylor et al., 2006; Tottenham et al., 2011; Dannlowski et al., 2012b; De Bellis et al., 2012; Garrett et al., 2012; Fonzo et al., 2013), pain (Noll-Hussong et al., 2010), non-traumatic olfactory (Croy et al., 2010) and traumatic memory (Lanius et al., 2001, 2003) processing reported altered activations of IFC, OFC, MPFC, DLPFC and VLPFC in maltreated individuals compared to healthy controls. The ACC, which forms part of the medial frontal cortex, has also consistently been shown to exhibit abnormal activation in maltreated individuals in various functions such as inhibitory control (Carrion et al., 2008; Mueller et al., 2010) as well as emotion (Tottenham et al., 2011; Dannlowski et al., 2012b; Fonzo et al., 2013), non-traumatic olfactory (Croy et al.,

2010) and traumatic memory (Lanius et al., 2001, 2003) processing compared to healthy controls.

Several studies of emotion and sensory processing have also consistently found enhanced activations of the limbic regions such as amygdala (Taylor et al., 2006; Croy et al., 2010; Maheu et al., 2010; Grant et al., 2011; McCrory et al., 2011, 2013; Tottenham et al., 2011; Dannlowski et al., 2012a, 2012b; De Bellis et al., 2012; Garrett et al., 2012; Fonzo et al., 2013; van Harmelen et al., 2013) and hippocampus (Croy et al., 2010; Maheu et al., 2010; Noll-Hussong et al., 2010; Garrett et al., 2012) in maltreated individuals compared to (healthy) controls. In addition, a few studies of inhibitory control (Muller et al., 2010) as well as emotion (McCrory et al., 2011; Dannlowski et al., 2012b; Garrett et al., 2012; Fonzo et al., 2013) and non-traumatic olfactory (Croy et al., 2010) processing also reported enhanced activation of the insula in maltreated individuals compared to healthy controls. The insula, classically considered a limbic region, is implicated in the processing of emotions and pain, as well as during situations requiring cognitive control (Singer et al., 2009; Menon and Uddin, 2010). It has been suggested that the anterior insula, together with the dorsal ACC, plays a role in the processing of saliency which is thought to respond to relevant stimuli in the environment and activate sympathetic responses in order to better prepare the individual to respond to the salient event (Critchley et al., 2005; Seeley et al., 2007; Menon and Uddin, 2010). Recent evidence suggests that the anterior insula is consistently engaged during both reflective orienting and motor inhibitions tasks (Hampshire et al., 2010; Swick et al., 2008; Boehler et al., 2010; Levy and Wagner, 2011). Hence, a dysfunction

of the insula in individuals with a history of childhood maltreatment may also underscore the inhibitory control and emotion processing deficits observed.

So far, only three studies (Dillon et al., 2009; Mehta et al., 2009; Muller et al., 2010) reported abnormal activation of the basal ganglia in individuals with a history of childhood maltreatment compared to healthy controls. Using the MID task that typically activates the ventral basal ganglia to investigate reward anticipation processing, adolescents who had experienced severe early deprivation showed hyporesponsive ventral striatum during reward anticipation (Mehta et al., 2009), while young adults with a history of childhood maltreatment displayed decreased anticipatory reward activity in the left putamen and globus pallidus (Dillon et al., 2009); thereby indicating that childhood maltreatment is associated with dysfunction in the basal ganglia implicated in reward and motivation processing. A study of inhibitory control found that adopted adolescents with early-life stress showed greater activation in the left IFC and striatum than healthy controls (Muller et al., 2010). These regions form the fronto-striatal neural network for inhibitory control (Rubia et al., 2003, 2007; Aron et al., 2004) which could account for the inhibitory deficits observed in maltreated individuals.

Additionally, altered activations of the cerebellum and cerebellar vermis associated with childhood maltreatment have also been observed in studies of emotion (Tottenham et al., 2011; Fonzo et al., 2013; MCrory et al., 2013) and non-traumatic olfactory (Croy et al., 2010) processing. Accumulating evidences suggest that besides motor control, the cerebellum also plays a role in affective and higher cognitive functions, in particular attention and timing functions (Rubia and Smith, 2004;

Schmahmann, 2004; Arnsten and Rubia, 2012). Hence, functional abnormalities of the cerebellum and cerebellar vermis associated with childhood maltreatment may underscore the attention and emotion processing deficits these individuals have.

Furthermore, these fronto-limbic and fronto-striatal-cerebellar regions which exhibited abnormal activation in individuals exposed to childhood maltreatment also showed aberrant functional connectivity patterns within the prefrontal-limbic-thalamic-cerebellar circuit, particularly in the salience and limbic emotional regulation networks (Cisler et al., 2013; Herringa et al., 2013; van der Werff et al., 2013a, b; Wang et al., 2013).

Therefore, the findings of abnormal activations and functional connectivity patterns of the prefrontal, limbic, striatal and cerebellar regions observed in these fMRI studies are in line with the sMRI findings of volumetric abnormalities in these regions (Chapter 3) suggesting that the fronto-limbic and fronto-striatal-cerebellar networks that mediate emotion, sensory and motivation processing as well as executive functions such as inhibitory control, attention and working memory are compromised in individuals who had experienced childhood maltreatment.

As with the sMRI studies reviewed (Chapter 3), fMRI studies of childhood maltreatment are also confounded by co-morbid psychiatric conditions (please see Table 4) except for five studies that used healthy participants with a history of childhood maltreatment (Taylor et al., 2006; Dannlowski et al., 2012a, 2012b; McCrory et al., 2011; 2013; Liu et al., 2012; Elton et al., 2013) and two studies with a matched

psychiatric control group (Grant et al., 2011; Wang et al., 2013). Although several studies used participants that were free of psychotropic medications (Taylor et al., 2006; Carrion et al., 2008; Maheu et al., 2010; Grant et al., 2011; Dannlowski et al., 2012a, 2012b; De Bellis et al., 2012; Garrett et al., 2012; Liu et al., 2012; Elton et al., 2013; van Harmelen et al., 2013) or medication free for at least 24 hours prior to scanning (Lanius et al., 2001, 2003; Mueller et al., 2010; Cisler et al., 2013; Fonzo et al., 2013), four studies (Dillon et al., 2009; Goff et al., 2013; Wang et al., 2013; van Harmelen et al., 2014) used participants who were taking medications such as SSRIs and there were a few studies that did not measure or report medication use of their participants (Raine et al., 2001; Mehta et al., 2009; Croy et al., 2010; Noll-Hussong et al., 2010; McCrory et al., 2011, 2013; Tottenham et al., 2011; Edmiston and Blackford, 2013; Herringa et al., 2013; Van der Werff et al., 2013a, b). This is a potential confound as medications such as SSRIs have been shown to affect brain function and alter activation using fMRI (Murphy, 2010). Moreover, numerous studies did not measure or control for drug abuse in participants (please see Table 4) even though drug abuse has been shown to affect brain function (Goldstein and Volkow, 2011). Also, it has been suggested that the sample size for fMRI studies should be ≥ 12 for result reliability (Desmond and Glover, 2002); hence, the findings of several relatively smaller studies (Raine et al., 2001; Noll-Hussong et al., 2010; Grant et al., 2011; De Bellis et al., 2012) should be viewed as preliminary. Lastly, most of the fMRI studies on childhood maltreatment used adult participants and only a few studies were conducted in children. It is crucial that more fMRI studies be conducted on paediatric samples as brain alteration can develop or normalize over time and the neural effects are likely to be different in adults versus children and adolescents.

TABLE 4. Summary of the Characteristics of fMRI Studies in Childhood Maltreatment

Article	Task	N (CM/HC)	Gender (M/F)	Children/ Adolescent/ Adult	Childhood Maltreatment Type	Comorbidities (maltreated group)	Medication (maltreated group)	ROI/ WBA	Drug Abuse
<i>Working Memory</i>									
Raine et al. (2001)	Visual/verbal working memory	9/9 (& 5 violent only)	23/0	Adult	PA	NR	NR	ROI	NR
<i>Inhibitory Control</i>									
Carrion et al. (2008)	Go/No-Go	16/14	13/17	Adolescent	PA, SA, WDV	PTSD (25%); Sub- PTSD (75%); MDD (19%); PD (6%); OCD (6%); ADHD (6%); enuresis (6%)	0	WBA	0
Mueller et al. (2010)	Stop-Change	12/21	14/19	Adolescent	N, non-specific M, >2 foster placements before adoption	Enuresis (8%); ODD (8%); GAD (8%); SP (16%)	8% (methylphenidateb ut stopped 30hrs prior)	WBA	NR
Elton et al. (2013)	Stop -- functional connectivity	40	19/21	Adult	PA, SA, EA, EN, PN	0	0	WBA	0
<i>Emotion Processing</i>									

Tottenham et al. (2011)	Emotional face Go/No-Go (fearful, neutral faces)	22/22	15/29	Children	Caregiver deprivation, EN	ADHD (23%); AD (15%); LD (15%); ODD (5%)	NR		ROI/WBA	NR
Maheu et al. (2010)	Emotional face-processing (angry, fearful, happy, neutral faces)	11/19	8/22	Adolescent	Caregiver deprivation, EN	SP (9%), SAD (9%), SoP (9%)	0		ROI	NR
Goff et al. (2013)	Emotional face-processing (fearful, happy, neutral faces)	38/31	33/36	Children / Adolescent	Caregiver deprivation, EN	21% exhibited mental characteristics within the clinical range for internalizing/externalizing problems and depression/total anxiety	11%		ROI	NR
De Bellis et al. (2012)	Emotional oddball (neutral, sad faces)	5/11	8/8	Adolescent	PA, N	MDD (60%); Dysthymia (20%); DDNOS (20%); PTSD (40%); ADHD (20%); ODD (20%)	0		ROI	30% (cannabis)
Grant et al.	Emotional	10/16 (&	15/21	Adult	PA, SA, EA,	MDD (100%)	0		ROI/	0

(2011)	selective attention (neutral, sad faces)	10 MDD only without trauma)			EN, PN			WBA	
van Harmelen et al. (2013)	Emotional face-processing (angry, fearful, happy, neutral, sad, faces)	60/75*	46/89	Adult	EA, EN	MDD (53%); AD (58%)	0	ROI/WBA	0
Edmiston & Blackford (2013)	Novel vs familiarized face-processing	18	6/12	Adult	PA, SA, EA, EN, PN	SoAD (28%); GAD (17%); SP (6%); ADNOS (11%); dysthymia (11%)	NR	ROI/WBA	NR
Garrett et al. (2012)	Emotional face-processing (angry, fearful, happy, neutral, sad faces)	23/23	21/25	Adolescent	PA, SA, WDV	PTSS (100%); MDD (22%); ADHD (4%); CD (4%); SAD (4%); PD (4%)	0	ROI/WBA	0
Fonzo et al. (2013)	Emotional face-matching (angry, fearful, happy faces)	16/17*	0/33	Adult	PA, SA, EA, EN, PN	PTSD (100%); MDD (55%); PD (27%); GAD (39%)	participants undergone washout for at least 4-6 weeks before scanning	ROI/WBA	0
McCrory et al. (2011)	Emotional face-processing	20/23	25/18	Children	PA, WDV	NR (Both groups had comparable levels of	NR	ROI	NR

	(angry, neutral, sad faces)					psychopathology symptoms)			
McCrory et al. (2013)	Masked dot-probe (angry, happy, neutral faces)	18/23	23/18	Children	PA, SA, EA, N	NR (Both groups had comparable levels of psychopathology symptoms)	NR	ROI/WBA	NR
Taylor et al. (2006)	Emotion observing and emotion labelling (angry, fearful faces)	30 (15 in high-risk group; 15 in low-risk group)	12/18	Adult	Risky childhood family environment including PA, EA, N, WDV	0	0	ROI	NR
Liu et al. (2012)	Emotional face-processing (fearful, happy, neutral faces)	23	13/10	Adolescent	Disadvantaged adolescents with various types of stressors including PA, SA, EA, EN, PN	0	0	ROI/WBA	0
Dannlowski et al. (2012a)	Emotional face matching (angry, fearful faces)	148	75/70	Adult	PA, SA, EA, EN, PN	0	0	ROI/WBA	NR
Dannlowski et al. (2012b)	Subliminal affective priming (happy, neutral, sad	150	63/71	Adult	PA, SA, EA, EN, PN	0	0	ROI/WBA	NR

faces)

Reward Processing

Mehta et al. (2009b)	Monetary incentive delay	12/11	12/11	Adolescent	Early deprivation including EN	NR	NR	ROI/ WBA	NR
Dillon et al. (2009)	Monetary incentive delay	13/29	20/22	Adult	PA, SA, EA	MDD (8%); Agoraphobia (8%); GAD (15%); PTSD (8%)	15% (citalopram, hydrocodone)	ROI	NR

Sensory Processing

Croy et al. (2010)	Non-traumatic olfactory (pleasant, neutral odour)	12/10*	0/22	Adult	PA, SA	DD (91.7%); AD (66.7%); OCD (16.7%); PTSD (50%); DiD (8.3%); SD (58.3%); ED (8.3%)	NR	ROI/ WBA	NR
Noll- Hussong et al. (2010)	Empathetic- pain-inducing visual paradigm	8/8*	2/14	Adult	SA	MPD (100%)	NR	WBA	NR

Traumatic Material Processing

Lanius et al. (2001)	Script-driven traumatic imagery	18^/0 ^ (9SA/MVA with PTSD,	NR	Adult	SA (61%), MVA (39%)	PTSD (50%); PTSD-subthreshold (50%); MDD	NR but participants undergone washout for at least 2 weeks	WBA	0 (substance use
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	(neutral, traumatic memory scripts)	9 SA/MVA with sub-PTSD)				(22%); Dysthymia (34%), PD (22%); Lifetime history of drug/alcohol abuse and dependence (66%); Current nicotine abuse (44%)	before scanning		disorder in remission >6 mths)
Lanius et al. (2003)	Script-driven traumatic imagery (anxious, neutral, sad, traumatic memory scripts)	20^/0 ^ (10 SA/MVA with PTSD, 10 SA/MVA with sub-PTSD)	NR	Adult	SA (65%), MVA (35%)	PTSD (50%); PTSD-subthreshold (50%); MDD (20%); Dysthymia (40%), PD (30%); Lifetime history of drug/alcohol abuse and dependence (60%); Current nicotine abuse (40%)	NR but participants undergone washout for at least 2 weeks before scanning	WBA	0 (substance use disorder in remission >6 mths)
<i>Social Exclusion</i>									
Van Harmelen et al. (2014)	Cyberball game	26/20	12/34	Adult	EA, EN	Depression (92%); SoP (54%); OCD (12%); GAD (4%); PTSD (50%)	42% (anti-depressant & anti-anxiogenic)	ROI/WBA	0
<i>Resting-State Functional Connectivity</i>									
Herringa et	Resting-state	64	34/30	Adolescent	PA, SA, EA,	NR	NR	ROI	NR

al. (2013)	functional connectivity				EN, PN				
Cisler et al. (2013)	Resting-state functional connectivity	26 [^] /12 [^] (19 abused + MDD; 7 abused only)	0/38	Adult	PA, SA, EA, EN, PN	MDD (73%); PTSD (38%)	Participants undergone washout for at least 2-4 weeks before scanning	ROI	0
Van der Werff et al. (2013a)	Resting-state functional connectivity	44/44*	42/46	Adult	EA (29.5%), EN (97.7%)	MDD (61%); AD (52%)	NR	ROI	NR
Van der Werff et al. (2013b)	Resting-state functional connectivity	22 [^] /11 [^] (11 abused + psychiatric problems; 11 abused only)	9/24	Adult	PA, SA, EA, EN	MDD (36%); AD (36%); PTSD (9%)	NR	ROI	NR
Wang et al. (2014)	Resting-state functional connectivity	18/20 (& 20 MDD only)	29/29	Adult	EN, PN	MDD (100%)	100% (antidepressant)	WBA	0

Abbreviations: N (CM/HC): Sample size (Childhood maltreatment group/Healthy control group); *: non-maltreated (but not healthy) control group; M/F: Male/Female; ROI/WBA: Region-of-Interest/Whole-Brain Analysis; PA: Physical abuse; SA: Sexual abuse; EA: Emotional abuse; EN: Emotional neglect; PN: Physical neglect; WDV: Witnessing domestic violence; N: Neglect; non-specific M: non-specific maltreatment; NR: Not reported; MDD: Major depressive disorder; PD: Panic disorder; OCD: Obsessive compulsive disorder; ODD: Oppositional defiant disorder; GAD: Generalized anxiety disorder; ADHD: Attention deficit hyperactivity disorder; SP: Specific phobia; PTSD: Post-traumatic stress disorder; SAD: Separation anxiety disorder; SoP: Social phobia; DDNOS: Depressive disorder not otherwise specified; AD: Anxiety disorder; LD: Learning disorders; MPD: Multisomatoform pain disorder; DD: Depressive disorders; DiD: Dissociative disorders; SD: Somatoform disorders; ED: Eating disorders; MVA: Motor vehicle accident; SoAD: Social anxiety disorder.

CHAPTER 5

The PhD Project: Neural Correlates of Physical Abuse in Childhood

As noted previously, one of the main limitations in the existing literature on the neural correlates of childhood maltreatment is the lack of control for psychiatric comorbidities which renders it unclear whether the neurobiological abnormalities can be attributed to childhood maltreatment or the associated psychiatric conditions or a combination of both. Therefore this PhD project aims to control for comorbid psychiatric conditions. Hence, an important question addressed in this PhD is: what is the effect of childhood maltreatment on the developing brain independently of these comorbidities and to what extent does the combination of childhood maltreatment and psychiatric disorders differ in its neurobiology from that of psychiatric disorders alone. Also, several studies employed ROI instead of WBA approach (please see Tables 3 & 4). The hypothesis-based nature of ROI may omit potential differences in regions that were not pre-specified (Friston et al., 2006). Furthermore, there are other limitations such as the confounding effects of medication and drug use, gender-unbalanced design and relatively small sample size.

5.1. Study Design

Therefore, this PhD project contributes to the existing research on childhood maltreatment by conducting the first meta-analysis of published whole-brain VBM studies of structural abnormalities in childhood maltreatment to elucidate the most robust volumetric GM abnormalities (Chapter 6). Next, it investigated the neurofunctional abnormalities associated with (severe) childhood physical abuse in three reasonably sized groups of age- and gender-matched young people ($N \geq 20$) using whole-brain fMRI analysis (Chapters 7-9) and adds on to the current fMRI

research on childhood maltreatment by 1) including a psychiatric control group that is matched on psychiatric comorbidities with the participants exposed to abuse to separate the confounding effects of comorbid psychiatric disorders, 2) controlling for medication and drug use by recruiting medication-naïve and drug-free young people, and 3) using rigorous assessment of childhood physical abuse by conducting the Childhood Experience of Care and Abuse (CECA) interviews additionally to substantiate the information from the Childhood Trauma Questionnaire (CTQ) and corroborating the abuse experience with social service records.

Furthermore, several studies have included participants with various forms of childhood maltreatment such as sexual, physical and emotional abuse, emotional and physical neglect, verbal abuse, early deprivation and witnessing domestic violence (please see Tables 3 & 4). Given that different types of childhood maltreatment differ in their clinical presentation; for instance, self-harm and eating disorders are more common in females who had been sexually abused (Weierich and Nock, 2008), it is conceivable that different types of maltreatment may also have different neurobiological, psychiatric and behavioural effects on the individual. For instance, childhood sexual abuse has different effects on brain structure (Heim et al., 2013) and has different psychiatric and behavioural consequences (Ackerman et al., 1998). It is thus crucial to examine the effects of various types of childhood maltreatment separately. This PhD project attempted to do this by examining the neural correlates of childhood physical abuse. However, it may be unrealistic to separate physical abuse from typically co-occurring emotional abuse and neglect (Edwards et al., 2003), as it is unlikely for the individual to experience (severe) physical abuse without experiencing at least moderate levels of emotional abuse and neglect

concurrently; on the other hand, physical abuse does not always co-occur with sexual abuse. Nonetheless, this project helps to extricate the influence of childhood sexual abuse on the findings by recruiting participants with a history of childhood physical abuse but without reported sexual abuse.

5.1.1. fMRI Tasks

Given the neuropsychological/fMRI evidences of deficits in inhibitory control (Mezzacappa et al., 2001; Beers and de Bellis, 2002; Navalta et al., 2006; Nolin and Ethier, 2007; DePrince et al., 2009; Samuelson et al., 2010; Carrion et al., 2008; Mueller et al., 2010), attention (Beer and De Bellis 2002; Nolin and Ethier 2007; DePrince et al., 2009; De Bellis et al., 2009; Pollak et al., 2010; Bucker et al., 2012; Gould et al., 2012; McDermott et al., 2012; Loman et al., 2013) and emotion processing (Pollak and Kistler, 2002; Pollak and Sinha, 2002; Pollak and Tolley-Schell, 2003; Wismer-Fries and Pollak, 2004; Pears et al., 2005; Pine et al., 2005; Vorria et al., 2006; Masten et al., 2008; Gibb et al., 2009; Caldwell et al., 2014; Koizumi et al., 2014; Taylor et al., 2006; Maheu et al., 2010; Grant et al., 2011; McCrory et al., 2011,2013; Tottenham et al., 2011; Dannlowski et al., 2012a, 2012b; De Bellis et al., 2012; Garrett et al., 2012; Liu et al., 2012; Edmiston et al., 2013; Fonzo et al., 2013; Goff et al., 2013; van Harmelen et al., 2013) in individuals with a history of childhood maltreatment, this PhD project selected 3 fMRI tasks that tap into the above functions: 1) a stop task to measure motor response inhibition and error processing (Chapter 7), 2) a sustained attention/vigilance task to measure sustained attention (Chapter 8) and 3) an emotion processing task (Chapter 9).

1) The Stop Signal Task

Although the go/no-go task has often been used to measure response inhibition and was used by Carrion et al (2008), it is worth noting that the task may involve several uncontrolled processes other than response inhibition such as selective attention and has a relatively lower load on inhibitory control than the stop task (Rubia et al., 2003). The stop signal paradigm (Schachar and Logan, 1990) is more specific and measures the ability to withhold an already triggered motor response to a go stimulus when it is followed unpredictably by a stop signal (Rubia et al., 2003). Hence, stop tasks have a higher load on inhibitory control than go/no-go tasks as they measure withholding of a triggered motor response about to be executed rather than selective inhibition that can be planned beforehand by selective attention to the stimuli (Rubia et al., 2001). As such, the two more recent fMRI studies on response inhibition in childhood maltreatment (Mueller et al., 2010; Elton et al., 2013) used the stop task instead. Another advantage of the stop task is that it also measures error processing, which is relevant to childhood maltreatment.

The tracking stop task used in this project thus measures successful and failed motor response inhibition. A tracking algorithm changes the time interval between go-signal and stop-signal onsets according to each participant's inhibitory performance to ensure that the task is equally challenging for everyone and to provide 50% successful and 50% unsuccessful inhibition (i.e. errors) trials at every moment of the task which allows the measurement of not only response inhibition but also error monitoring.

Although no fMRI study to-date has examined error-related brain activation in childhood maltreatment, it is plausible that individuals exposed to (severe)

childhood physical abuse may exhibit abnormally enhanced error-related brain activation due to the constant need to monitor their actions in order to avoid potential painful mistakes that are often associated with violence in an abusive context. Studies of error monitoring have focused particularly on the error-related negativity (ERN), an event-related potential (ERP) component, associated with action monitoring/error detection localized to the medial frontal cortex/ACC/supplementary motor area (SMA) (Gehring et al., 1993). Enhanced ERN has been associated with high sensitivity to punishments, hypervigilance (Santesso et al., 2011) and common comorbidities of childhood maltreatment including depression and anxiety (Olvet and Hajcak, 2008). It is further suggested that environmental adversity and punitive parental behaviour, which are often considered etiological factors for various internalizing disorders, might be linked to increases in ERN, which has also been repeatedly associated with these disorders (Meyer et al., 2014). Furthermore, maltreated children receive more negative evaluative and affective feedback from their parents which predispose them to experience more shame when they fail on tasks (Alessandri and Lewis, 1996). Maltreated individuals also tend to avoid threat (Pine et al., 2005) and exhibit heightened neural reactivity to threat-related faces (Dannlowski et al., 2012a; McCrory et al., 2011, 2013) and their hypersensitivity to punishment is associated with increased risk-taking to avoid potential punishments (Weller and Fisher, 2013). Thus, given that punishment and punitive parenting lead to lasting enhanced ERN (Riesel et al., 2012; Meyer et al., 2014); persistent harsh punishment experiences in childhood may possibly sensitize the child to errors and lead to overactive error monitoring.

In healthy children and adults, brain activation correlating with successful inhibitory control include predominantly right IFC, SMA, caudate, subthalamic nucleus and cerebellum (Aron and Poldrack, 2006; Li et al., 2006; Rubia et al., 2003; 2005, 2007, 2008, 2013; Sharp et al., 2010; Vink et al., 2005; Woolley et al., 2008). Brain activation correlating with unsuccessful inhibitory control (error detection) include most prominently the MPFC, including the ACC and pre-SMA/SMA as well as lateral prefrontal regions (Li et al., 2008; Rubia et al., 2003, 2005, 2007, 2008, 2011, 2013; Sharp et al., 2010; Woolley et al., 2008).

2) The Sustained Attention Task (SAT)

Despite neuropsychological findings of attention deficits in maltreated individuals (Beer and De Bellis 2002; Nolin and Ethier 2007; DePrince et al., 2009; Pollak et al., 2010; Bucker et al., 2012), no fMRI study has as yet examined brain activation in sustained attention or any other attention function in this group. Sustained attention is the ability to direct and maintain consistent focus on specific stimuli (DeGangi and Porges, 1990) and is a key executive function thought to underpin many 'higher' attentional processes such as selective and divided attention and other general cognitive ability (Sarter et al., 2001). During sustained attention, healthy children and adults show activation in the dorsal and ventral attention systems, comprising DLPFC and VLPFC, respectively, inferior parieto-temporal regions, ACC and striato-thalamic regions, as measured in the Continuous Performance Test (Hager et al., 1998; Carter et al., 2001; Rubia et al., 2009a; 2009b; Smith et al., 2011) or vigilance tasks of rapid visual/auditory information processing (Lawrence et al., 2003; Voisin et al., 2006). However, for the purpose of greater specificity of assessing sustained attention functions, this PhD project selected a

parametric sustained attention/vigilance task (Christakou et al., 2013; Murphy et al., 2014), where the load on sustained attention is progressively increased, in order to assess the effect of attention load on brain activation. Activation in healthy children and adults include a bilateral network of the dorsal and ventral attention networks, comprising DLPFC, IFC, SMA, cingulate, striato-thalamic, parietal-temporal and cerebellar regions (Christakou et al., 2012; Murphy et al., 2014).

(3) The Emotion Processing Task (EPT)

Facial expressions of emotion are important signals that guide social interactions. Facial perception, defined as “any higher-level visual processing of faces” (Kanwisher et al., 1997), involves both perceptual processing and recognition of emotional meaning of a stimulus (Adolphs, 2002). Although some basic emotions (e.g. happy, sad, anger, fear) have been shown to be universal and can be reliably recognized from facial expressions (Adolphs, 2002), the growing number of fMRI studies on face perception indicate contrasting findings (Neumann et al., 2008) and are not yet able to definitely characterize the brain regions associated with each specific emotion (Fusar-Poli et al., 2009). In a recent meta-analysis of fMRI studies on facial emotional processing (Fusar-Poli et al., 2009), the processing of faces was associated with increased activation in a number of visual areas (fusiform, lingual, inferior and middle occipital gyri), limbic areas (amygdala, insula, parahippocampal gyrus), temporo-parietal areas (parietal lobule, middle and superior temporal gyri), medial frontal gyrus, putamen and the cerebellum. Compared with neutral faces, processing fearful faces was associated with neural activation in the bilateral amygdala, fusiform gyrus and MPFC. Angry faces activated the left insula and right

inferior occipital gyrus; sad faces activated the right amygdala and left lingual gyrus; and happy faces activated the bilateral amygdala, left fusiform gyrus and right ACC.

The emotion processing task used in this project was designed by Prof Rubia and Dr Hart to measure the ability to recognise and discriminate between dynamic facial expressions of basic emotions (angry, fearful, sad, happy and neutral). Clips have been taken from a validated set of stimuli (Simon et al., 2008) and are cut backward from the peak of the expression to avoid different lengths and variability of exposure to the visual stimuli. Participants had to discriminate between the valence of the emotions (positive, neutral or negative) which also allowed us to test whether the group with a history of abuse perceived the neutral expressions as negative, which may possibly stem from a hypervigilance to negative facial expressions as has been reported in patients with depression (Maniglio et al., 2014) and social anxiety (Cooney et al., 2006).

Therefore, based on the literature reviewed, there is evidence that the maltreated individuals have deficits in the function and structure of the brain regions that mediate these tasks, i.e. in the PFC (DLPFC, MPFC, OFC, VLPFC), ACC, amygdala, striato-thalamic, parietal lobes and cerebellum. Thus, structural abnormalities in these PFC regions, which are involved in the top-down control of cognition and emotion, may underlie the observed deficits in inhibitory control, attention and emotion processing through their fronto-striatal (inhibition), fronto-striato-thalamo-cerebellar (sustained attention) and fronto-limbic (emotion processing) connections. This PhD project therefore investigated neurofunctional abnormalities in these disorder-relevant functional domains.

5.2. Hypotheses

It is hypothesized that relative to both healthy and psychiatric controls, young people with a history of (severe) childhood physical abuse will have:

fMRI Dysfunctional Activation

- 1) enhanced activation in inferior frontal areas of inhibitory control during successful response inhibition in the stop task.
- 2) enhanced activation in typical error monitoring regions of the MPFC/ACC and pre-SMA/SMA during inhibition failures in the stop task.
- 3) reduced activation in typical dorsal and ventral fronto-striato-thalamo-cerebellar sustained attention regions especially during higher loads of attention in the SAT.
- 4) enhanced activation in fronto-limbic areas comprising vmPFC, amygdala, insula and ACC during negative emotions, in particular to fear and anger, in the EPT.

Behavioural Performance

- 1) poorer inhibition (i.e. longer stop signal reaction time) in the stop task.
- 2) longer post-error reaction time in the stop task, reflecting increased slowing down after making mistakes.
- 3) more omission errors during higher loads of attention in the SAT.
- 4) shorter reaction times in the fear and angry face trials in the EPT.

The correlation between brain activation and abuse measures such as severity, duration and age at onset of abuse will be examined as exploratory analyses. It is hypothesised that there will be a correlation between the above hypothesised behavioural and brain activation deficits and the abuse measures.

Gray Matter Abnormalities in Childhood Maltreatment: A Voxel-Wise Meta-Analysis

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Objective: Childhood maltreatment acts as a severe stressor that produces a cascade of physiological and neurobiological changes that lead to enduring alterations in brain structure. However, structural neuroimaging findings have been inconsistent. The authors conducted a meta-analysis of published whole-brain voxel-based morphometry studies in childhood maltreatment to elucidate the most robust volumetric gray matter abnormalities relative to comparison subjects to date.

Method: Twelve data sets were included, comprising 331 individuals (56 children/adolescents and 275 adults) with a history of childhood maltreatment and 362 comparison subjects (56 children/adolescents and 306 adults). Anisotropic effect size-signed differential mapping, a voxel-based meta-analytic method, was used to examine regions of smaller and larger gray matter volumes in maltreated individuals relative to comparison subjects.

Results: Relative to comparison subjects, individuals exposed to childhood

maltreatment exhibited significantly smaller gray matter volumes in the right orbitofrontal/superior temporal gyrus extending to the amygdala, insula, and parahippocampal and middle temporal gyri and in the left inferior frontal and postcentral gyri. They had larger gray matter volumes in the right superior frontal and left middle occipital gyri. Deficits in the right orbitofrontal-temporal-limbic and left inferior frontal regions remained in a subgroup analysis of unmedicated participants. Abnormalities in the left postcentral and middle occipital gyri were found only in older maltreated individuals relative to age-matched comparison subjects.

Conclusions: The findings demonstrate that the most consistent gray matter abnormalities in individuals exposed to childhood maltreatment are in relatively late-developing ventrolateral prefrontal-limbic-temporal regions that are known to mediate late-developing functions of affect and cognitive control, which are typically compromised in this population.

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Individual differences in social, behavioral, and cognitive functioning result from a combination of genetic and environmental influences on brain development. Development of the brain, a highly plastic organ, is regulated by genes but sculpted by environmental experiences (1). Animal studies have shown that environmental factors have an important impact on different aspects of brain development, including the number of neurons, glial cells, dendrites, and synapses; myelination; and neurotransmitter and growth factor activity, all of which underlie behavior (2).

There is an increasing interest in understanding the effects of early environmental adversity on the developing brain. Childhood maltreatment, which may include physical, sexual, and emotional abuse as well as neglect, is common in the United Kingdom, with prevalence rates of 6.9% for severe physical abuse, 4.8% for sexual abuse, and 9.8% for severe emotional and physical neglect (3). Childhood maltreatment has been associated with a host of neurocognitive consequences, such as low academic performance and IQ and deficits in emotion and reward

processing, attention, and inhibitory control (4). Large-scale epidemiological studies have reported that childhood adversities, including childhood maltreatment, are significantly associated with first onsets of a wide range of psychiatric disorders over the life course, notably mood, anxiety, and substance use disorders (5, 6).

The human brain continues its development during childhood through processes of synaptic remodeling, activity-dependent myelination, and programmed cell death, which affect the organization of both gray and white matter (7). Neural plasticity due to experience is substantial, with gray matter being less heritable and more affected by early environment than white matter (8). For instance, children from low-income households have smaller and slower growth trajectories in parietal and frontal gray matter volumes than children from middle- and high-income households despite there being no difference at birth, and these trajectories are related to greater behavior problems (9). Also, early stress and exposure to traumatic events has been shown to adversely

This article is discussed in a Video by Dr. Pine.

affect the nature and trajectory of normal brain development (4), particularly in late-developing frontal, temporal, and basal ganglia structures (10, 11).

A better understanding of the neurobiological consequences of childhood maltreatment will indirectly inform our understanding of how early-life adversities can lead to the emergence of psychiatric conditions. It may also lead to heightened awareness of maltreatment's biological consequences to brain development and lead to better prevention strategies and targeted treatment to reverse the experience-induced neurobiological abnormalities in those affected.

Modern neuroimaging methods such as MRI have revealed smaller volumes in several brain regions in individuals exposed to childhood maltreatment relative to unexposed comparison subjects, including the prefrontal cortex, hippocampus, amygdala, anterior cingulate cortex, corpus callosum, and cerebellum (12), suggesting that fronto-limbic areas may be the most compromised. However, the majority of studies have used a region-of-interest analysis approach, testing predominantly for frontal and limbic abnormalities (13–17).

Examining previously defined regions of interest limits the search to regions hypothesized a priori, thereby providing a biased and inappropriately constrained characterization of anatomy (18). Hence, studies are increasingly using whole-brain analysis and have reported gray matter volume deficits in areas similar to those identified by region-of-interest studies in maltreated individuals, such as the prefrontal cortex (including the dorsolateral prefrontal, orbitofrontal, and medial prefrontal cortices) and the temporal and anterior cingulate cortices, as well as other areas not commonly examined in region-of-interest studies, such as the thalamus, the insula, and the parietal and occipital cortices (19–25). Only one region-of-interest study (26), on intimate partner violence, reported an association between smaller occipital gray matter volume and childhood maltreatment. Whole-brain-analysis studies have also reported larger gray matter volumes for some areas identified by region-of-interest studies in maltreated individuals, such as the cerebellum and the prefrontal, posterior cingulate, and superior temporal cortices, as well as areas not commonly examined in region-of-interest studies, such as the occipital and parahippocampal gyri (13, 21). In addition, similar to region-of-interest studies that, with the exception of one study (14), found no basal ganglia deficits (16, 27), only two whole-brain-analysis studies reported basal ganglia deficits in healthy individuals exposed to childhood maltreatment (22, 23). Abnormalities in limbic areas have also been observed, but mostly in region-of-interest studies. Thus, abnormalities of the amygdala and the glucocorticoid receptor-rich hippocampus have commonly been found in region-of-interest studies of childhood maltreatment (15, 16, 28–32), but only two whole-brain-analysis studies have reported deficits in the hippocampus (31, 33) and none have reported deficits in the amygdala.

Given this variability in the literature, our aim in this preliminary meta-analysis of whole-brain voxel-based

morphometry studies of structural abnormalities in childhood maltreatment was to determine which areas are most consistently affected in these maltreated individuals across studies that used whole-brain imaging analyses.

Method

Study Selection

Using PubMed, ScienceDirect, Web of Knowledge, and Scopus, we conducted a comprehensive literature search of studies published up to January 2014 that used whole-brain morphometric comparisons between individuals exposed to childhood maltreatment and unexposed comparison subjects. The search terms were “childhood maltreatment,” “child abuse,” and “early stress” or “childhood adversities” plus “structural gray matter,” “voxel-based morphometry,” or “whole-brain.” Studies that used fewer than 10 patients were excluded. In some cases, we obtained from the study authors additional details essential for the meta-analysis (i.e., peak coordinates) that were not included in the original publications. In our analyses, we followed the guidelines from the Meta-Analysis of Observational Studies in Epidemiology group (34).

Comparison of Regional Gray Matter Volume

Regional differences in gray matter volume between individuals exposed to childhood maltreatment and unexposed comparison subjects were analyzed using the Anisotropic Effect Size version of the Signed Differential Mapping (Anisotropic ES-SDM) software package (www.sdmproject.com), which employs a voxel-based meta-analytic approach that is based on, and improves on, other existing methods (35, 36). Anisotropic ES-SDM uses the reported peak coordinates and effect sizes to recreate, based on the spatial correlation between neighboring voxels, brain maps of the effect size of the volume differences between individuals exposed to childhood maltreatment and comparison subjects, rather than just assessing the probability or likelihood of a peak, and accounts for sample size and variance as well as between-study heterogeneity. These unique features make SDM an optimal method for comparing two groups without biasing the results toward those brain regions that show more interstudy heterogeneity.

The SDM methods have been described in detail elsewhere (35, 36) and are briefly summarized here. First, peak coordinates and effect sizes (derived, for example, from *t* values) of gray matter differences between maltreated individuals and comparison subjects were extracted from each data set. Notably, those peaks that did not appear statistically significant at the whole-brain level were excluded; that is, while different studies may employ different thresholds, we ensured that the same statistical threshold throughout the brain was used in each study. This was intended to avoid biases toward liberally thresholded brain regions, which is common for regions of interest. Second, a standard Montreal Neurological Institute map of the differences in gray matter was separately recreated for each study by means of an anisotropic Gaussian kernel, which assigns higher effect sizes to the voxels more correlated with peaks. This anisotropic kernel has been found to optimize the recreation of the effect size maps, and at the same time it is robust because it does not depend on a full width at half maximum (36). Third, a map of the effect size variance was derived for each study from its effect size map and its sample size. Fourth, the mean map was obtained by voxel-wise calculation of the random-effects mean of the study maps, weighted by the sample size and variance of each study and the between-study heterogeneity.

In addition, a jackknife sensitivity analysis was conducted to assess the reproducibility of the results by iteratively repeating

TABLE 1. Demographic and Clinical Characteristics of the 12 Voxel-Based Morphometry Studies Included in the Meta-Analysis^a

Study	Exposed to Childhood Maltreatment (N=331)						
	N	Mean Age (Years)	% Male	Comorbid Disorders	Maltreatment Types ^b	Onset Age (Years)	Duration (Years)
Child/adolescent samples							
Carrion et al. (13)	24	11.0	58	PTSD, 50%; sub-PTSD, 50%; depression, 17%; social phobia, 13%; ADHD, 13%; separation anxiety disorder, 8%; generalized anxiety disorder, 8%; simple phobia, 8%	WV, PA, SA, EA, PN	NR	NR
De Brito et al. (24)	18	12.0	61	0 ^c	PA, N, SA, EA	1.9–5	2.7–7.3
Liao et al. (25)	14	17.0	50	Generalized anxiety disorder, 100%	PA, SA, EA, EN, PN	NR	NR
Adult samples							
Tomoda et al. (40)	23	21.7	65	ADHD, 4%	HCP	3.9	8.5
Tomoda et al. (19)	23	20.2	0	Major depression, 17%; PTSD, 17%; depersonalization disorder, 4%	SA	2–15	4.1
van Harmelen et al. (41)	84	38.7	35	Major depression, 77%; anxiety disorders, 68%	EN, EA	NR	NR
Landré et al. (39)	17	24.9	0	PTSD, 100%; major depression, 47%; suicidal risk, 65%; agoraphobia, 19%; addiction, 6%	SA	NR	NR
Thomaes et al. (31)	31	35.3	0	PTSD, 100%; other anxiety disorders, 70%; major depression, 64%; eating disorders, 8%; other mood disorders, 9%; borderline personality disorder, 33%; cluster C personality disorder, 30%	SA, PA	NR	NR
Tomoda et al. (42)	21	21.2	43	mood disorders, 48%; anxiety disorders, 24%	PVA	NR	NR
Tomoda et al. (20)	22	21.8	27	Major depression, 41%; anxiety disorders, 32%; PTSD, 18%; eating disorders, 9%; personality disorders, 5%	WDV	NR	9.8
Chaney et al. (33)	30	41.7	57	Major depression, 67%; healthy control, 33%	PA, SA, EA, EN, PN	NR	NR
Sheffield et al. (43)	24	41.7	33	Psychotic disorders, 100%; anxiety disorders, 46%; PTSD, 29%; OCD, 17%; panic disorder, 8%; eating disorder, 8%; generalized anxiety disorder, 4%	SA	NR	NR

^a ADHD=attention deficit hyperactivity disorder; NR=not reported; OCD=obsessive-compulsive disorder; PTSD=posttraumatic stress disorder; SSRIs=selective serotonin reuptake inhibitors.

^b Types of maltreatment: EA=emotional abuse; EN=emotional neglect; HCP=harsh corporal punishment; N=neglect; PA=physical abuse; PN=physical neglect; PVA=parental verbal abuse; SA=sexual abuse; WDV=witnessed domestic violence; WV=witnessed violence.

^c Participants in the De Brito et al. study (24) all reported no psychiatric diagnoses and are matched on anxiety, depression, and PTSD symptoms.

the same analysis, excluding one data set at a time to establish whether the results remained significant (37). Similarly, a heterogeneity analysis was conducted to determine whether there was significant unexplained between-study variability within the results (35). Finally, we conducted a subgroup analysis on studies

that used unmedicated participants only, as well as meta-regression analyses with age and gender as regressors (37). Statistical significance was determined using standard randomization tests, thus creating null distributions from which p values can be directly obtained (35).

Exposed to Childhood Maltreatment (N=331)			Unexposed Comparison Subjects (N=362)			
Mean IQ	Medications	N	Mean Age (Years)	% Male	Comorbid Disorders	Mean IQ
90.0	Stimulants and/or SSRIs, 21%	24	11.0	58	0	105
103.7	0	20	12.6	50	0	109.2
NR	0	12	16.7	50	Generalized anxiety disorder, 100%	NR
119.5	0	22	21.7	27	0	118.7
NR	0	14	19.0	0	0	NR
NR	0	97	36.6	33	Major depression, 43%; anxiety disorders, 41%	NR
NR	0	17	24.7	0	0	NR
NR	Fluoxetine, 64%; benzodiazepines, 48%	28	35.2	0	0	NR
119	0	19	21.1	37	0	122.8
120.2	0	30	21.6	27	0	123.6
NR	SSRIs, 32%, venlafaxine or mirtazapine, 12%	53	36.3	32	Major depression, 32%; healthy control, 68%	NR
94.7	Chlorpromazine, 93%	26	38.2	50	0	103.7

Results

Included Studies and Sample Characteristics

The search yielded 17 studies, five of which were excluded: two of these computed correlations within a maltreated sample only, without a comparison group (22, 23); one study was part of a larger study on family risk for depression that included only four individuals who experienced emotional abuse (29); one genetic study on childhood adversity

consisted of 11% of childhood maltreatment cases while most participants had experienced other stressors, such as moving house and death of a parent (38); and one study used a tensor-based morphometry analysis (21). Thus, 12 studies were included in the final meta-analysis, comprising 331 individuals exposed to childhood maltreatment and 362 comparison subjects. Of the 12 studies, nine consisted of adult and three of child/adolescent samples. Overall, the studies included 581 adults (306 comparison

subjects) and 112 children/adolescents (56 comparison subjects). Nine of the studies included males and females, and three (19, 31, 39) included only females. All studies excluded participants with substance abuse or medical conditions that could adversely affect growth and development. All except one study (24) included maltreated individuals with psychiatric comorbidities, and eight studies recruited only unmedicated participants. The studies examined various forms of childhood maltreatment, including sexual, physical, and emotional abuse; neglect; witnessed domestic violence; parental verbal abuse; and harsh corporal punishment. No significant differences in age were found between participants exposed to childhood maltreatment and comparison subjects, reflecting the group matching in the original studies. Table 1 summarizes the participants' demographic and clinical characteristics. All studies had received ethical approval from their respective ethics boards.

Regional Differences in Gray Matter Volume

Data were obtained from all 12 studies included in the meta-analysis. As shown in Table 2 and Figure 1, individuals exposed to childhood maltreatment, relative to unexposed comparison subjects, had significantly smaller gray matter volumes in the right orbitofrontal/superior temporal gyrus extending to the amygdala, insula, and parahippocampal and middle temporal gyri and in the left inferior frontal, left postcentral, and right middle temporal gyri. They had larger gray matter volumes in the right superior frontal and left middle occipital gyri. However, the larger volumes in these regions should be interpreted with caution, as they were driven by one study (33).

Reliability and Subgroup Analyses

Jackknife sensitivity analyses revealed that the deficits in the right orbitofrontal/superior temporal gyrus were highly robust, as they were replicable in all 12 studies; abnormalities in the left postcentral, left middle occipital, and right superior frontal gyri were highly replicable, as they remained significant in 11 combinations of studies, and smaller volume of the left inferior frontal gyrus remained significant in 10 combinations of studies. (Details of the analysis are provided in Table S1 in the online data supplement.)

Analysis of heterogeneity showed that there was significant unexplained between-study variability in the right orbitofrontal/superior temporal, left inferior frontal, and postcentral gyri.

In the subgroup analysis of unmedicated participants, the deficits in the right orbitofrontal/superior temporal, left inferior frontal, and right middle temporal gyri remained, and no regions were enhanced in volume.

Meta-Regression Analyses: Effects of Age and Gender

Information on both age and gender was available for all 12 data sets. Using a stringent threshold of $p < 0.0005$ to minimize spurious findings, age was negatively correlated with left postcentral occipital gray matter volume ($x = -56$,

$y = -10$, $z = 26$; SDM value = -2.15 , $p = 0.00005$; 255 voxels) and positively correlated with left middle occipital gray matter volume ($x = -14$, $y = -94$, $z = 14$; SDM value = 1.79 , $p = 0.00007$; 368 voxels). Smaller postcentral and larger middle occipital gray matter volumes were found in older but not younger maltreated individuals relative to age-matched comparison subjects. There were no significant gender differences.

Discussion

To our knowledge, this is the first preliminary meta-analysis of whole-brain voxel-based morphometry studies in childhood maltreatment. Maltreated individuals, relative to comparison subjects, exhibited significantly smaller gray matter volumes in the right orbitofrontal/superior temporal gyrus extending to the amygdala, insula, and parahippocampal and middle temporal gyri and in the left inferior frontal, postcentral, and right middle temporal gyri. They also had larger gray matter volumes in the right superior frontal and left middle occipital gyri. Deficits in the right orbitofrontal-temporo-limbic and left inferior frontal regions remained in the subgroup analysis of unmedicated participants. Age was negatively correlated with left postcentral and positively correlated with left middle occipital gray matter volumes.

These whole-brain meta-analysis findings highlight the detrimental effects of childhood maltreatment on several brain regions, including the ventral prefrontal, temporal, and limbic regions, consistent with previous region-of-interest and whole-brain-analysis structural imaging studies. Although many of the previous whole-brain-analysis studies did not directly report abnormalities in the amygdala and hippocampus, four of the included studies (24, 31, 33, 43) reported clusters that included the right amygdala/parahippocampal gyrus, although their peaks, as in this study, were located in nearby regions.

The findings thus demonstrate that childhood maltreatment is associated with abnormalities in the right orbitofrontal-temporo-limbic regions that form the paralimbic system, which is known to be implicated in affect and motivational processing and the self-regulation of social-emotional behaviors (44–46). Maltreated individuals also exhibited deficits in the left inferior frontal gyrus, which is part of the ventral attention system and a key area of cognitive control (47), mediating saliency detection, action selection, switching, inhibition, and sustained attention (48–50).

The abnormalities in the paralimbic network of affect control in the maltreated individuals could possibly be related to the typical development of common psychiatric comorbidities, particularly depression and posttraumatic stress disorder (PTSD), which have also been associated with gray matter abnormalities in these orbitofrontal and limbic regions (51, 52).

The meta-analytic association between childhood maltreatment and structural abnormalities in these regions is further underpinned by findings of direct correlations

TABLE 2. Gray Matter Volume Differences in Participants Exposed to Childhood Maltreatment Relative to Unexposed Comparison Subjects^a

Cluster Peak (Size)	Cluster Breakdown (Brodmann's Area; Size)	Local Maxima			
		Region (Brodmann's Area)	MNI Coordinates	SDM Value	p ^b
Participants with childhood maltreatment < comparison subjects					
Right orbitofrontal/ superior temporal gyrus (506 voxels)	Right superior temporal gyrus (BA 38; 283 voxels)	Right superior temporal gyrus (BA 38)	32, 12, -26	-1.556	0.0005
	Right inferior orbitofrontal gyrus (BA 47; 67)	Right parahippocampal gyrus (BA 36)	30, -6, -30	-1.219	0.004
	Right insula (37 voxels)				
	Right middle temporal gyrus (BA 21; 31 voxels)				
	Right amygdala (18 voxels)				
	Right parahippocampal gyrus (BA 36; 11 voxels)				
Left inferior frontal gyrus (131 voxels)	Left inferior frontal gyrus (BA 44/45; 80 voxels)	Left inferior frontal gyrus (BA 45)	-44, 18, 12	-1.384	0.002
	Left inferior frontal gyrus (BA 45; 49 voxels)	Left inferior frontal gyrus (BA 44)	52, 12, 6	-1.27	0.003
Left postcentral gyrus (625 voxels)	Left postcentral gyrus (BA 43/4/3/2; 482 voxels)	Left postcentral gyrus (BA 43)	-60, -10, 20	-1.555	0.0005
	Left precentral gyrus (BA 4/3/5; 139 voxels)	Left postcentral gyrus (BA 43)	-60, -12, 30	-1.555	0.0005
		Left postcentral gyrus (BA 43)	-58, -14, 26	-1.555	0.0005
Right middle temporal gyrus (61 voxels)	Right middle temporal gyrus (BA 21/22; 60 voxels)	(BA 21)	60, -34, 0	-1.285	0.003
Participants with childhood maltreatment > comparison subjects					
Right superior frontal gyrus (106 voxels)	Right superior frontal gyrus (BA 9; 44 voxels)	Right superior frontal gyrus (BA 9)	16, 68, 18	1.128	0.0003
	Right medial superior frontal gyrus (BA 10; 62 voxels)				
Left middle occipital gyrus (162 voxels)	Left middle occipital gyrus (BA 18; 108 voxels)	Left middle occipital gyrus (BA 18)	-28, -66, 32	1.139	0.0002
	Left inferior parietal gyrus (BA 40; 20 voxels)	Left middle occipital gyrus (BA 18)	-30, -60, 34	1.139	0.0002
	Left angular gyrus (BA 39; 14 voxels)				
	Left superior occipital gyrus (BA 19; 7 voxels)				

^a BA=Brodmann's area; MNI=Montreal Neurological Institute; SDM=Signed Differential Mapping.^b Uncorrected p.

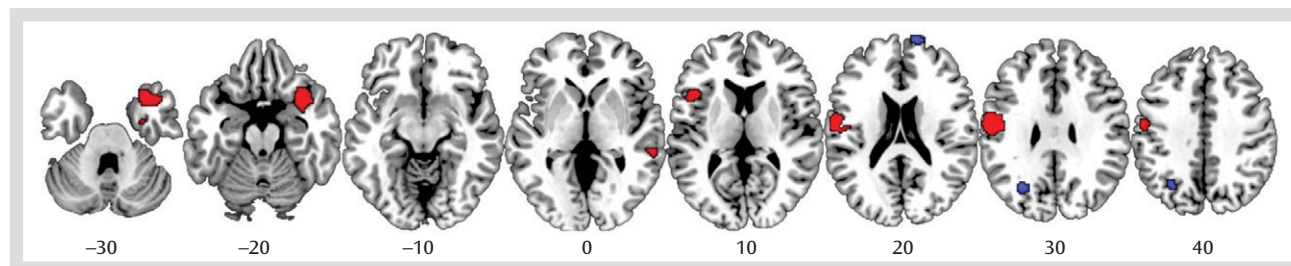
between severity or duration of maltreatment and brain volumetric abnormalities in these regions in individual studies. For instance, left inferior prefrontal volume was negatively correlated with sexual abuse severity (43). Amygdala volumes were inversely associated with time spent in institutions (15) and positively associated with age at adoption (16) in severely deprived children/adolescents. Hippocampal volumes were negatively correlated with duration (53) and severity (30) of childhood maltreatment. Left and right occipital volumes were negatively correlated with the duration of the childhood sexual abuse that occurred before age 12 (19). Furthermore, large-sample studies using whole-brain regression analysis in healthy adolescents and adults also reported a correlation between childhood maltreatment exposure and smaller corticostriatal-limbic gray matter volumes (22, 23).

Therefore, it is likely that the abnormalities we observed here in the orbitofrontal-temporo-limbic regions, which

mediate affect control, and in the left inferior frontal gyrus, which mediates cognitive control, underlie the consistently observed neuropsychological deficits associated with childhood maltreatment, such as emotion and reward processing (54, 55), attention, and inhibitory control (56, 57).

This relationship is further supported by functional MRI (fMRI) studies of childhood maltreatment finding abnormal activations in orbitofrontal-limbic regions during affect processing and in inferior frontal regions during response inhibition and attention tasks. For instance, predominantly right amygdala and insula hyperresponsiveness to negative facial expressions has consistently been observed in maltreated children/adolescents (58–60) and adults (61) relative to healthy subjects, together with lower orbitofrontal activation in severely deprived children (62) and healthy adults exposed to childhood physical abuse (63), suggesting a deficit in their emotion-regulation abilities. Also, in a recent large correlational fMRI study

FIGURE 1. Regions of Gray Matter Volume Differences in Participants Exposed to Childhood Maltreatment Relative to Unexposed Comparison Subjects^a



^a Slices are shown in axial view and marked with the z coordinate as distance in millimeters from the anterior-posterior commissure. The right side of the image corresponds to the right side of the brain. Smaller volumes are indicated in red and larger volumes in blue.

of healthy adults, childhood maltreatment scores were strongly correlated with right amygdala and insula responsiveness to fearful/angry (23) and sad (64) faces. Women with sexual abuse-related PTSD exhibited overactivation of the left inferior frontal gyrus, which was absent in healthy subjects, during the processing of trauma-related words (65). In cognitive inhibition tasks, adopted adolescents who experienced childhood maltreatment showed greater activation in the left inferior frontal gyrus than did healthy subjects (66). Finally, resting-state functional connectivity studies have also reported lower prefrontal-limbic connectivity in individuals exposed to childhood maltreatment compared with healthy subjects (67–69), and this lower connectivity has in turn been found to mediate the development of internalizing symptoms (68). Thus, the structural findings of orbitofrontal-limbic and inferior frontal deficits in childhood maltreatment may be associated with the observed functional abnormalities in the same regions during affect and cognitive control, respectively.

Interestingly, the meta-regression analysis showed an age effect on smaller postcentral gray matter volume that was observed only in older maltreated participants. Childhood maltreatment has been associated with abnormal development of the sensory systems that relay adverse sensory experiences. For instance, women who experienced childhood sexual and emotional abuse had thinner left somatosensory cortex surrounding the regions representing the clitoris and the face, respectively, which suggests that the developing brain may adapt to shield the child by sensory gating of abusive experiences (70). Thus, decreased somatosensory volume may represent atrophy due to childhood maltreatment and may not manifest until adulthood, as found in the present meta-analysis.

The human brain is a highly plastic organ that is continually modified by experience and undergoes changes in structure and function across the lifespan. Given that the orbitofrontal, inferior frontal, and superior temporal gyri develop relatively late (by late adolescence) (10, 71, 72), these regions may be more susceptible to impairment in individuals with early adversities. Diffusion tensor imaging

studies have shown that the orbitofrontal-temporo-limbic white matter tracts that mediate affect control and the inferior frontal-temporal white matter tracts that mediate complex cognitive functions, such as executive functioning and attention, are late developing, beyond childhood and adolescence, and reach their maturity in mid-adulthood (73, 74). Thus, our meta-analytic finding of an association between childhood maltreatment and gray matter abnormalities in regions that form these late-developing orbitofrontal-temporo-limbic affective and inferior frontal cognitive networks suggests an environmentally triggered disturbance in the normal development of these networks that may underlie the cognitive and emotional problems that develop as a consequence of early adversities. Furthermore, the findings were not confounded by medication, as they survived the subgroup analysis of unmedicated participants. Finally, childhood maltreatment may also affect and delay the normal development of the sensory regions, although the abnormalities may not manifest until adulthood.

Limitations

This meta-analysis has several limitations, some of which are inherent to meta-analyses. First, it was based on peak coordinates and effect sizes from published studies, rather than raw statistical brain maps, and this approach may result in less accurate results (35). Second, different studies used different statistical thresholds. Third, while voxel-wise meta-analytic methods provide excellent control for false positive results, false negative results are more difficult to avoid (35). Fourth, there are some inherent limitations to the voxel-based morphometry method, such as reduced effectiveness in detecting spatially complex and subtle group differences (75). Fifth, we were unable to assess whether age at onset or duration of childhood maltreatment was associated with any of the reported structural changes because the included studies did not report that information.

Among other limitations is the heterogeneity of maltreatment types included in most studies of neglect and sexual, physical, and emotional abuse, which makes it

impossible to disentangle the specific effect of each type of maltreatment on the brain. It is plausible that exposure to single types of maltreatment, depending on the nature of the abusive experience, is associated with more specific alterations in regions that are crucial to the perception and processing of the adverse experience, whereas exposure to multiple forms of maltreatment is more commonly associated with morphological alterations in cortico-limbic regions (20, 70). Also, all except one study included maltreated participants with comorbid psychiatric conditions, making it impossible to determine the specific effect of childhood maltreatment independent of psychiatric comorbidities. All studies were cross-sectional, and hence the meta-analytic findings are still correlational. The included studies also differed in their recruitment criteria, with some studies recruiting maltreated participants meeting criteria for specific psychiatric disorders (13, 25, 31, 33, 39, 41, 43) and others recruiting maltreated participants regardless of psychiatric outcome (19, 20, 24, 40, 42); the latter approach is more likely to provide an unbiased perspective of the effects of childhood maltreatment. However, a strength is that all the studies excluded participants with substance abuse and medical conditions that could adversely affect growth and development. Also, it must be noted that there was between-study heterogeneity in nearly all main findings of the meta-analysis. Meta-regression analyses allowed us to explain some of this variability; for example, we found that older but not younger maltreated individuals had smaller postcentral gray matter volumes relative to age-matched comparison subjects. The remaining heterogeneity should be viewed with some caution, because heterogeneity may be overestimated in SDM when peaks from the different studies are spatially very close to a voxel, as individual study effect size estimates are either very large (i.e., similar to those of the peaks) or null (i.e., in studies without peaks close to the voxel). Lastly, meta-analytic results may change in the future as more studies using whole-brain-analysis methods are included.

Conclusions

Our meta-analytic findings show that the most consistent structural abnormalities in childhood maltreatment are in right orbitofrontal-temporo-limbic and left inferior frontal regions, which likely underlie the observed deficits in affect and cognitive control. Insights into the neurobiological abnormalities associated with early environmental adversities such as childhood maltreatment are important, as they emphasize the devastating consequences of early environmental adversities on brain development. Hopefully, such findings will aid in future developments to minimize environmental risk in early life and to develop strategies that strengthen resilience as well as treatments to normalize these experience-induced morphological alterations.

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TABLE S1. Results of the Subgroup and Jackknife Sensitivity Analyses^a

Brain Region	Studies Using Unmedicated Participants (N=8)	Jackknife Analysis: Excluded Study												
		Summary	Car 2009	DeB 2013	Liao 2013	Tom 2009a	Tom 2009b	Har 2010	Lan 2010	Tho 2010	Tom 2010	Tom 2012	Cha 2013	She 2013
Childhood maltreatment < comparison subjects														
Right orbitofrontal/superior temporal gyrus	Yes	12/12	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Left inferior frontal gyrus	Yes	10/12	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Left postcentral gyrus	No	11/12	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Right middle temporal gyrus	Yes	10/12	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Childhood maltreatment > comparison subjects														
Right superior frontal gyrus	No	11/12	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Left middle occipital gyrus	No	11/12	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

^a “Yes” indicates that the brain region remains significantly different in the subgroup/jackknife analysis; “No” indicates that the brain region is no longer significantly different in the subgroup/jackknife analysis. Car 2009=Carrion et al., 2009; De B 2013=De Brito et al., 2013; Liao 2013=Liao et al., 2013; Tom 2009a=Tomoda et al., 2009a; Tom 2009b=Tomoda et al., 2009b; Har 2010=Harmelen et al., 2010; Lan 2010=Landre et al., 2010; Tho 2010=Thomaes et al., 2010; Tom 2010= Tomoda et al., 2010; Tom 2012=Tomoda et al., 2012; Cha 2013=Chaney et al., 2013; She 2013=Sheffield et al., 2013

CHAPTER 7

Neural Correlates of Error Processing in Young People with a History of Severe Childhood Abuse

7.1. Introduction

There is increasing interest in understanding the effects of early environmental adversities on the developing brain. Childhood maltreatment, including physical, sexual and emotional abuse, and neglect, is common in the United Kingdom with paediatric prevalence rates of 6.9% for severe physical abuse, 4.8% for sexual abuse and 9.8% for severe neglect (NSPCC, 2011). Childhood adversities are furthermore significantly associated with first onsets of various psychiatric disorders including mood, anxiety and PTSD (Green et al., 2010).

The psychopathological outcomes associated with childhood maltreatment may be mediated by the disruption of cognitive processes and their associated neural underpinnings (Bremner and Vermetten, 2001). Childhood maltreatment has been associated with many adverse cognitive consequences such as low IQ and academic performance as well as impaired attention, inhibition, emotion and reward processing (Pechtel and Pizzagalli, 2011). Notably, cognitive control deficits have been reported in children who had been maltreated (DePrince et al., 2009; Mezzacappa et al., 2001) and institutionalized (Beckett et al., 2010; Pollak et al., 2010) and in adults who had experienced childhood sexual abuse (Navalta et al., 2006).

Cognitive control, particularly the ability to monitor one's ongoing performance and detect errors, is a key cognitive function critical to adaptive behaviour (Nachev et al., 2008). Substantial improvement in cognitive control and

error monitoring occurs from childhood to early adulthood with progressively increasing fronto-striatal activation with increasing age underlying the development of error-regulatory networks, which are important for adult-level cognition (Rubia, 2013; Rubia et al., 2007; Velanova et al., 2008).

Studies of error monitoring have focused particularly on the error-related negativity (ERN), an ERP component, associated with action monitoring/error detection localized to the medial frontal cortex/ACC/SMA (Gehring et al., 1993). Enhanced ERN has been associated with high sensitivity to punishments, hypervigilance (Santesso et al., 2011) and common comorbidities of childhood maltreatment including depression and anxiety (Olvet and Hajcak, 2008). It is further suggested that environmental adversity and punitive parental behaviour, which are often considered etiological factors for various internalizing disorders, might be linked to increases in ERN, which has also been repeatedly associated with these disorders (Meyer et al., 2014).

Furthermore, the ability to detect errors and adjust behaviour accordingly may be especially crucial in abusive contexts where mistakes are often associated with harsh punishment. Maltreated children receive more negative evaluative and affective feedback from their parents which predispose them to experience more shame when they fail on tasks (Alessandri and Lewis, 1996). Individuals with a history of childhood maltreatment also tended to avoid threat (Pine et al., 2005) and exhibit heightened neural reactivity to threat-related faces (Dannlowski et al., 2012; McCrory et al., 2011; McCrory et al., 2013) and their hypersensitivity to punishment is associated with increased risk-taking to avoid potential punishments (Weller and

Fisher, 2013). Thus, given that punishment and punitive parenting lead to lasting enhanced ERN (Meyer et al., 2014; Riesel et al., 2012); persistent harsh punishment experiences in childhood may possibly sensitize the child to errors and lead to overactive error monitoring.

Structural MRI studies report that childhood maltreatment is associated with significant deficits in the lateral and ventromedial fronto-limbic areas and networks (Hart and Rubia, 2012; Lim et al., 2014). Our recent meta-analysis showed that the most consistent GM deficits are in relatively late-developing inferior frontal and orbitofronto-limbic and temporal regions that mediate late-developing cognitive control and affect, respectively (Lim et al., 2014). However, relatively few fMRI studies are published in childhood maltreatment and only three studies (Carrion et al., 2008; Elton et al., 2013; Mueller et al., 2010) examined inhibitory networks. During successful inhibition, youths exposed to childhood abuse had increased activation in inferior, medial frontal and ACC relative to healthy controls (Carrion et al., 2008; Mueller et al., 2010). In adults, however, maltreatment was associated with no change in brain activation but decreased functional connectivity of the IFC and dorsal ACC (Elton et al., 2013).

Therefore, this study examined the association between severe childhood (physical) abuse and neural networks of inhibitory control and error processing in medication-naïve, drug-free young people using a challenging tracking stop task, which ensures 50% inhibition failures and is hence optimally suited to test for error detection networks. Sexual abuse was excluded as it has different effects on brain structure (Heim et al., 2013) and different behavioural and psychiatric consequences

(Ackerman et al., 1998). To assess the specificity of the association with childhood abuse, a third group of psychiatric controls that matched the participants who had experienced childhood abuse on psychiatric comorbidities was included. It is hypothesized that the participants with a history of abuse, relative to both healthy and psychiatric controls, would have abnormally increased activation in typical error monitoring regions of the dorsomedial frontal cortex including the ACC and pre-SMA/SMA (Bonini et al., 2014; Ridderinkhof et al., 2004; Sharp et al., 2010) as well as in inferior frontal areas of inhibitory control.

7.2. Method

7.2.1. Procedure and Participants

Young people who experienced childhood physical abuse before the age of 12 years old were first recruited through social services and psychiatric clinics. Next, for all the participants exposed to childhood abuse, we requested signed permission from the young people and/or their parents/legal guardian to contact their respective social services to confirm that there were official records of physical abuse, including documents of child protection orders and court appearances. Only participants with formal records of physical abuse were invited to participate in the subsequent interviews and scans. Information from the Childhood Experience of Care and Abuse (CECA) and the Childhood Trauma Questionnaire (CTQ) were consistent with the official records.

Seventy (23 individuals who had experienced childhood abuse, 20 psychiatric controls, 27 healthy controls) right-handed, medication-naïve, drug-free and age-matched young people were initially assessed by a child psychiatrist using the

Development and Well-Being Assessment (DAWBA) (Goodman et al., 2000) designed to generate ICD-10 and DSM-IV psychiatric diagnoses. The Strengths and Difficulties Questionnaires (SDQ) (Goodman and Scott, 1999) and Beck's Depression Inventory (BDI) (Beck et al., 1988) were used to provide symptom scores on psychopathology. IQ was assessed using Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). The Childhood Trauma Questionnaire (CTQ) (Bernstein and Fink, 1998) a 25-item retrospective self-report questionnaire to measure the severity of childhood physical, sexual and emotional abuse, and physical and emotional neglect was administered. Each of the five subscales has a possible range of 5 to 25. Socioeconomic status (SES) was measured by two non-sensitive items from the Family Affluence Scale (FAS) (Currie et al., 1997) on housing tenure and room occupancy.

Twenty-three young people who had experienced childhood physical abuse before the age of 12 years old were recruited through social services and psychiatric clinics. They scored ≥ 13 on the CTQ physical abuse subscale and the abuse history was corroborated by social service records and Childhood Experience of Care and Abuse (CECA) interviews (Bifulco et al., 1994). Psychiatric comorbidities included PTSD, depression, anxiety, conduct disorder and phobia. One participant was excluded due to motion artefacts, leaving a final sample of 22 participants.

Twenty psychiatric patients matched with the participants exposed to abuse on psychiatric comorbidities but with no history of childhood maltreatment (scored < 8 for physical abuse, < 9 for emotional abuse, < 6 for sexual abuse, < 10 for emotional neglect, < 8 for physical neglect on the CTQ) were recruited through psychiatric

clinics and social services. PTSD patients experienced non-abuse related trauma (e.g. bullying, lived in the Afghanistan during wartime, witnessed a murder, experienced a car accident or the death of a loved one). Three participants were excluded due to motion artefacts, leaving a final sample of 17 psychiatric controls.

Twenty-seven healthy controls with no history of psychiatric illness and childhood maltreatment (scored < 8 for physical abuse, < 9 for emotional abuse, < 6 for sexual abuse, < 10 for emotional neglect, < 8 for physical neglect on the CTQ) were recruited through advertisements in the same geographic areas of South London to ensure similar socioeconomic background.

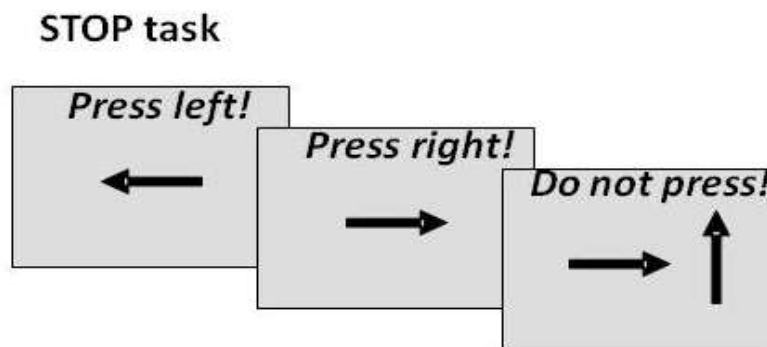
Exclusion criteria for all participants were childhood sexual abuse, learning disability, neurological abnormalities, epilepsy, drug abuse, $IQ < 70$, and the usual MRI contraindications. Urine tests were conducted using the 10 panel T-cup urine test (<http://www.testfield.co.uk>) to detect recent drug use. Participants' informed consent (and parental consent where age appropriate) and approval from the local Ethical Committee were obtained.

7.2.2. fMRI Paradigm: Stop Task

The rapid, mixed trial, event-related fMRI design was practiced by participants once before scanning. The visual tracking stop task requires withholding a motor response to a go stimulus when it is followed unpredictably by a stop signal (Rubia et al., 2013; Rubia et al., 2003; Rubia et al., 2007). The basic task is a choice reaction time task (left and right pointing arrows: go signals) with a mean inter-stimulus interval of 1.8s (234 go trials). In 20% of trials, pseudo-randomly

interspersed, the go signals are followed (about 250ms later) by arrows pointing upwards (stop signals), and participants have to inhibit their motor responses (60 stop trials). A tracking algorithm changes the time interval between go-signal and stop-signal onsets according to each participant's inhibitory performance to ensure that the task is equally challenging for everyone and to provide 50% successful and 50% unsuccessful inhibition trials at every moment of the task (Figure 7.1). Brain activation to the failed stop and successful stop trials is contrasted with the implicit baseline go trials.

FIGURE 7.1. Schematic Presentation of the tracking Stop Task



Participants have to respond to go arrows that point either right or left with a right/left button response. In 20% of trials, the go-signals are followed (about 250ms later) by stop signals and subjects had to inhibit their motor responses. A tracking algorithm changes the time interval between go-signals and stop-signals according to each subject's performance on previous trials (average percentage of inhibition over previous stop trials, recalculated after each stop trial), resulting in 50% successful and 50% unsuccessful inhibition trials.

7.2.3. Performance Data Analysis

Multiple Analysis of Variance (ANOVAs) were used to compare the main variables of the stop task performance among the three groups using SPSS 16: stop-

signal reaction time, mean reaction time to go trials, post-error reaction time, omission errors and the probability of inhibition to stop trials. *P* values were Bonferroni-adjusted for multiple comparisons.

7.2.4. fMRI Image Acquisition

Gradient echo echo-planar MR imaging (EPI) data were acquired on a 3T GE Signa HDx system at the Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London. Stimuli were projected on a screen, visible through prism in the scanner. The body coil was used for RF transmission and an 8-channel head coil for RF reception. During the 9-minute run of the task, in each of 28 non-contiguous planes parallel to the anterior-posterior commissural, 296 T₂*-weighted MR images depicting Blood Oxygen Level Dependent (BOLD) contrast covering the whole brain were acquired with: echo time (TE) = 30ms, repetition time (TR) = 1.8s, 28 slices, flip angle = 75°, in-plane resolution = 3.75mm², field of view (FOV) = 240mm, slice thickness/gap = 5/0.5mm, matrix = 64 x 64. A high-resolution gradient echo EPI dataset was also acquired for accurate spatial normalization (TE = 30ms, TR = 3s, 43 slices, flip angle = 90°, in-plane resolution = 1.875mm², FOV = 240mm, slice thickness/gap = 3/0.3mm, matrix = 128 x 128).

7.2.5. fMRI Image Analysis

Image preprocessing and whole-brain analyses were carried out using Statistical Parametric Mapping software (SPM8, www.fil.ion.ucl.ac.uk/spm). Data were realigned to correct for subject movement and co-registered to the high-resolution gradient EPI, which was then used to estimate the parameters for spatially

normalizing the data into a standard anatomical space (Montreal Neurological Institute). The resulting normalized volume time series was spatially smoothed using a Gaussian kernel of 8-mm full width at half maximum.

Data were analysed within the framework of the general linear model. A single-subject (first-level) model was created for each participant, including regressors encoding failed stop and successful stop trials. Movement parameters from the realignment procedure were included in the model as regressors of no interest. For second-level (group) analyses, contrast images from the first-level analyses were used to conduct full factorial whole-brain analyses for each condition. BOLD responses are reported using a stringent cluster threshold of $p < 0.05$ family-wise error rate (FWE) corrected and voxel threshold of $p < 0.001$ for within-group activations for the two contrasts. Given the limited studies aimed at specifying brain differences in childhood abuse populations, and to control for the false positive rate (using $p < 0.05$ FWE-corrected cluster statistics) while limiting potential Type II errors, an a-priori cluster-forming threshold of $p < 0.01$ for significant between-group differences was chosen.

Additionally, regions showing significant group differences were extracted using MARSBAR (Brett et al., 2002) and defined using spherical masks with a radius of 6mm around the peak coordinates for subsequent correlational analyses. These regions were selected to represent the main differences for confirmatory analyses on the influence of potential confounds such as IQ and task performance and for exploratory analyses examining the relationship with abuse measures.

7.3. Results

7.3.1. *Participant Characteristics*

The groups did not differ significantly in age, gender, ethnicity or SES, but did differ in IQ, as expected (Table 7.1). Since lower IQ is associated with childhood maltreatment (De Bellis et al., 2009; Nolin and Ethier, 2007), artificially matching groups on IQ is inappropriate as it creates unrepresentative groups; either the childhood abuse group will have higher IQs than the population with childhood abuse or the control group will have IQs below normative expectations (Dennis et al., 2009). Also, it is misguided to control for IQ differences by covarying for IQ when groups are not randomly selected and the covariate is a pre-existing group difference that did not occur by chance, as ANCOVA would lead to potentially spurious results (Dennis et al., 2009; Miller and Chapman, 2001). The primary data analyses are therefore presented without matching or covarying for IQ. However, to rule out any potential influence of IQ, additional confirmatory analyses including an ANCOVA covarying for IQ and correlational analyses of IQ with brain activation and performance measures within each group were also conducted.

Although the study selected participants with severe childhood physical abuse, they also experienced marked/severe childhood emotional abuse and neglect (Table 7.1) which typically co-occur with physical abuse, and hence are a representative group of the population with childhood abuse (Edwards et al., 2003; Trickett et al., 2011).

Healthy controls scored significantly lower on BDI ($p < 0.01$) and all SDQ difficulties subscales ($p < 0.001$) than the participants who had experienced abuse, and on BDI ($p < 0.001$), SDQ emotional problems ($p < 0.001$) and hyperactivity ($p <$

0.05) subscales than psychiatric controls. Participants exposed to abuse scored significantly higher than psychiatric controls on SDQ conduct ($p < 0.01$) and peer problems ($p < 0.05$) but lower on prosocial ($p < 0.01$) subscales (Table 7.1).

7.3.2. Task Performance

Mean performance values are reported in Table 7.2. The probability of inhibition was about 50% in all participants with no significant group differences, showing that the task algorithm was successful ($F(2, 63) = 0.86$; $p = 0.43$).

Groups differed significantly on mean reaction time to go trials ($F(2, 63) = 3.59$; $p < 0.03$) and post-error reaction time ($p < 0.02$) but not on stop-signal reaction time ($p = 0.16$). Post-hoc analyses showed that the participants who had experienced abuse were significantly slower in their responses on both measures than healthy controls ($p < 0.05$).

7.3.3. Brain Activation

Motion

Multivariate ANOVA (MANOVA) showed no significant group differences in maximum translation ($F(6,122) = 1.34$, $p > 0.05$) or rotation ($F(6,122) = 0.40$, $p > 0.05$) parameters.

TABLE 7.1. Demographic Characteristics of 22 Young People Exposed to Childhood Abuse, 17 Psychiatric Controls and 27 Healthy Controls

	Childhood Abuse (N=22)		Psychiatric Controls (N= 17)		Healthy Controls (N=27)		Analysis		Between Groups
	Mean	SD	Mean	SD	Mean	SD	F(2, 63)	p (corr.)	
Age (years)	17.2	2.44	17.0	2.42	17.5	1.63	0.28	0.75	-
[age range:13-20]									
Socioeconomic status	2.77	0.69	2.94	0.66	3.22	0.75	2.53	0.09	-
IQ	91.7	15.2	94.7	13.2	105.4	10.1	7.73	0.001	CA, PC < HC
SDQ:									
<i>Emotional problems</i>	4.50	2.82	5.24	2.99	1.92	1.61	10.9	<0.001	CA, PC > HC
<i>Conduct problems</i>	4.32	2.08	2.12	2.03	1.68	1.60	12.5	<0.001	CA > PC, HC
<i>Hyperactivity</i>	5.36	2.36	4.47	2.58	2.84	2.14	7.06	0.002	CA, PC > HC
<i>Peer problems</i>	3.73	1.61	2.18	1.78	1.16	1.72	13.4	<0.001	CA > PC, HC
<i>Prosocial</i>	7.27	1.72	8.71	1.69	8.08	1.41	3.96	0.02	CA< PC
<i>Total difficulties score</i>	17.9	6.56	14.0	6.57	7.60	5.73	16.3	<0.001	CA, PC > HC
Beck's Depression Inventory	16.4	10.4	22.3	12.1	5.92	6.09	9.49	< 0.001	CA, PC > HC
CTQ:									
<i>Physical abuse</i>	21	4.16	6.06	1.35	5.52	0.94	133.2	<0.001	CA > PC, HC
<i>Emotional abuse</i>	17.8	4.21	7.0	1.62	6.04	1.13	258.7	<0.001	CA > PC, HC
<i>Sexual abuse</i>	5.14	0.66	5.47	1.07	5.11	0.42	1.49	0.23	-
<i>Physical neglect</i>	13.8	5.23	6.65	2.32	5.59	1.22	42.3	<0.001	CA > PC, HC

<i>Emotional neglect</i>	17.9	4.74	9.12	3.66	7.93	3.35	40.6	<0.001	CA > PC, HC
Age at onset of (physical) abuse (years)	4.05	2.73							
Duration of (physical) abuse (years)	8.27	3.12							
	N	%	N	%	N	%	χ^2	<i>p</i>	Between Groups
Gender (Males)	15	68	8	47	21	77	4.46	0.11	-
Ethnicity:							7.91	0.10	-
<i>Caucasian</i>	10	45	3	18	13	48			
<i>Afro-Caribbean</i>	9	41	8	47	12	44			
<i>Others (Asian/mixed)</i>	3	14	6	35	2	8			
Psychiatric diagnosis:									
<i>PTSD</i>	13	59	12	70	-				
<i>Depression</i>	6	27	6	35	-				
<i>Anxiety disorders</i>	5	23	5	29	-				
<i>Social phobia</i>	1	5	1	6	-				
<i>ADHD</i>	1	5	1	6	-				
<i>ODD/CD/Other disruptive behaviours</i>	5	23	4	23	-				

Abbreviations: CA=Childhood Abuse; PC=Psychiatric Controls; HC=Healthy Controls; corr=Bonferroni corrected; CTQ=Childhood Trauma Questionnaire; SDQ=Strength and Difficulties Questionnaire; ADHD=Attention Deficit Hyperactivity Disorder; PTSD=Post-Traumatic Stress Disorder; ODD=Oppositional Defiant Disorder; CD=Conduct Disorder

TABLE 7.2. Stop Task Performance of 22 Young People Exposed to Childhood Abuse, 17 Psychiatric Controls and 27 Healthy Controls

	Childhood Abuse (N=22)		Psychiatric Controls (N= 17)		Healthy Controls (N=27)		Analysis		
Performance Measure	Mean	SD	Mean	SD	Mean	SD	F(2, 63)	p (corr.)	Between Groups
Stop signal RT (msec) ^a	132	158	192	116	117	106	1.86	0.16	-
Stop signal delay	425	180	319	127	370	150	2.27	0.11	-
Go signal RT (msec)	557	97	511	94	487	87	3.59	0.03	CA > HC
Post-error RT (msec)	576	129	527	102	487	97	3.98	0.02	CA > HC
Probability of inhibition (%)	52	7	51	2	50	3	0.86	0.43	-
Omission errors to go signals	16	25	7	10	5	11	2.87	0.06	-

Abbreviations: CA=Childhood Abuse; PC=Psychiatric Controls; HC=Healthy Controls; corr=Bonferroni corrected; RT=Reaction Time

^a Calculated by subtracting the mean stop signal delay (the average time between go and stop signal, at which the participant managed to inhibit to 50% of trials) from the mean reaction time to go trial.

Failed Stop-Go Contrast

Within-group brain activations

Both healthy controls and participants who had experienced abuse activated similar clusters of bilateral IFC, ACC, inferior, middle and superior temporal gyri, supramarginal, inferior parietal, middle occipital and fusiform gyri, cerebellum, right middle, superior frontal gyri and left superior parietal gyri; while the participants exposed to abuse activated additional clusters of bilateral pre-/postcentral gyri, PCC and inferior occipital cortices, cerebellar vermis, left hippocampus and precuneus. The psychiatric controls also activated similar but relatively smaller clusters of bilateral inferior and middle temporal gyri, supramarginal, inferior parietal gyri and left superior temporal, middle occipital and fusiform gyri (Table 7.3 & Figure 7.2).

Between-group brain activations

For failed inhibition, ANOVA showed a significant group effect in a cluster comprising bilateral pre-SMA/SMA, dorsal ACC, superior frontal gyri and left paracentral lobule. Post-hoc comparisons showed that the participants with a history of abuse had increased activation in these regions relative to healthy controls and in some voxels within the SMA compared to psychiatric controls. Psychiatric and healthy controls did not differ from each other. Given my hypothesis that young people who had experienced abuse would have increased error-related activation compared to both control groups, further planned group comparisons showed that they had increased activation in a slightly larger cluster of the above regions and additionally the bilateral precentral, right postcentral and middle frontal gyri relative to healthy controls and in some voxels within the SMA compared to psychiatric controls (Table 7.4, Figures 7.3 & 7.4).

TABLE 7.3. Regions of Brain Activation during Failed Stop versus Go Response Trials for 22 Young People Exposed to Childhood Abuse, 17 Psychiatric Controls and 27 Healthy Controls

Brain Region	BA	Cluster Level		Peak MNI Coordinates	Voxel Level
		No. of Voxels	<i>p</i> (corr.)		<i>Z</i>
<u>Healthy Controls</u>					
Right inferior/middle/superior temporal/supramarginal/ inferior/superior parietal/angular/middle occipital/ fusiform gyri	37/19/20/21/37/22/39/40/7	4452	<0.0001	56,-56,40	5.53
				54,-28,-8	5.38
				62,-52,0	5.26
Left inferior/middle/superior temporal/supramarginal/ inferior/superior parietal/angular/middle occipital/ fusiform gyri	19/37/39/22/40/7	1856	<0.0001	-58,-54,34	4.88
				-58,-42,38	4.82
				-50,-64,46	4.70
Right lingual/fusiform gyri/cerebellum	19	1425	<0.0001	28,-56,-30	4.50
				20,-54,-6	4.45
				28,-44,-22	4.43
Right middle/superior frontal gyri	46/10/9/8/6	1195	0.001	22,52,34	5.47
				14,18,64	4.71
				16,36,48	4.46
Right inferior frontal/middle/superior temporal gyri	47/21/38/22	852	0.005	40,14,-12	5.44
				34,4,-24	3.16
Bilateral anterior cingulate cortex /medial frontal gyrus	32/24/9	668	0.014	0,30,24	5.27

Left middle/superior frontal gyri	9/8/10	633	0.017	-30,50,28 -22,46,36	4.93 4.67
Left cerebellum	-	594	0.021	-36,-58,-28 -20,-60,-28	4.16 4.14
Left inferior frontal/superior temporal gyri	47/38	509	0.033	-42,18,-12 -36,2,-18	4.73 3.44

Childhood Abuse

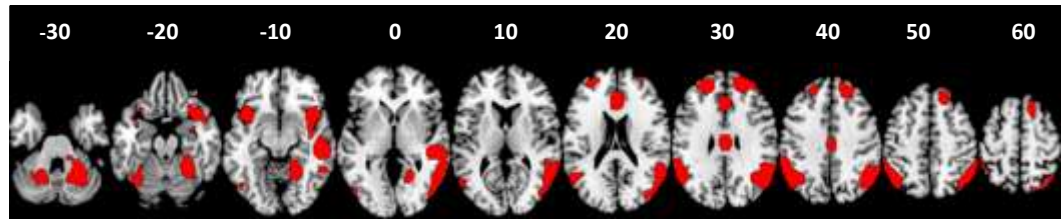
Left inferior frontal/inferior/middle/superior temporal gyri/ hippocampus/precentral/postcentral/supramarginal/ inferior/superior parietal gyri/precuneus/ inferior/middle occipital/fusiform gyri/cerebellum/vermis	47/44/37/21/20/39/38/22/42/ 6/4/3/1/2/40/7/18/19/36	8536	<0.0001	-32,-54,-30 -50,-74,-6 -42,18,-12	5.93 5.12 5.00
Right inferior frontal/inferior/middle/superior temporal/ precentral/postcentral/supramarginal/inferior parietal/ inferior/middle occipital/fusiform gyri/cerebellum/vermis	47/37/19/21/20/22/39/38/12/ 6/4/2/1/3/40/18	6452	<0.0001	32,-56,-32 62,-52,14 46,18,-8	4.53 5.09 5.06
Left inferior/middle/superior frontal gyri Bilateral anterior cingulate cortex/medial frontal gyrus	46/10/9/8/6/32/24	3065	<0.0001	-34,46,28 -30,42,36 0,32,28	5.83 5.07 4.92
Right middle/superior frontal gyri	10/46/9/8/6	1539	<0.0001	42,40,30 42,8,58 44,44,20	4.48 4.47 4.24

Bilateral posterior cingulate cortices	23/31/24	537	0.029	2,-24,32 -8,-10,34	4.47 3.38
<u>Psychiatric Controls</u>					
Right supramarginal/inferior/superior parietal/angular gyri	40/19/39/7	1204	0.001	48,-62,42 52,-50,38 58,-40,48	4.57 4.14 3.47
Left inferior/middle temporal/middle occipital/fusiform gyri	19/37/21/22/39/18	969	0.003	-44,-72,6 -56,-56,12 -44,-70,-8	4.23 3.99 3.88
Right inferior/middle temporal gyri	37/20/21	617	0.018	58,-32,-6 62,-50,-2	4.29 4.09
Left superior temporal/supramarginal/inferior parietal/angular gyri	39/40	591	0.021	-54,-54,34 -40,-58,60 -38,-46,42	4.21 3.47 3.23

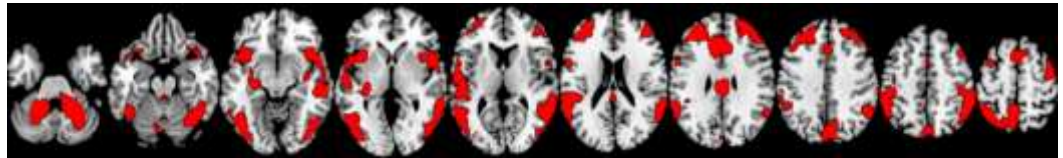
Abbreviations: MNI= Montreal Neurological Institute; corr=FWE-corrected; BA=Brodmann's Area

FIGURE 7.2. Brain Activation during Failed Stop versus Successful Go Response Trials

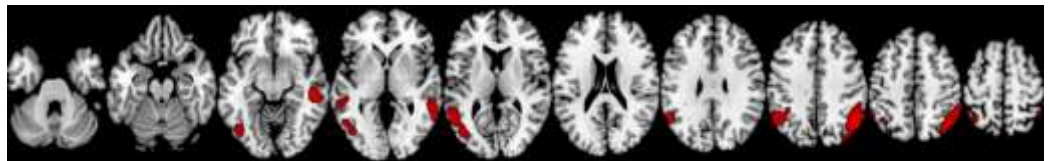
1) Healthy Controls



2) Childhood Abuse



3) Psychiatric Controls



Axial sections of brain activation during failed stop versus successful go response trials for 1) healthy controls, 2) participants exposed to childhood abuse and 3) psychiatric controls, $p < 0.05$, FWE-corrected at cluster level. Axial slices are marked with the z coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

For the cluster of significant group differences, a spherical mask with radius 6mm around the peak voxel (-2,-4, 74) was defined and BOLD response was extracted for correlational analyses with IQ and performance measures within each group, and with abuse measures within the group of participants who had experienced abuse only. There were no significant correlations.

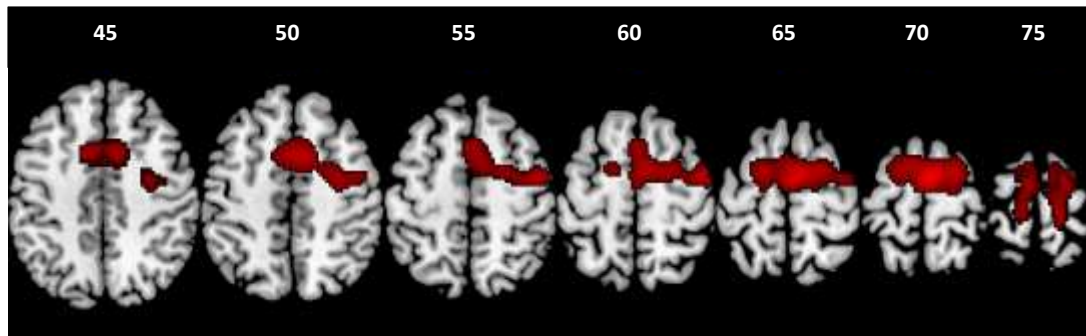
Given that the participants with a history of abuse had significantly lower IQ than healthy controls, data were re-analysed covarying for IQ (Figure 7.5). All main findings remained significant. Also within each group, IQ did not correlate significantly with brain activation in areas of group differences or with performance measures. Therefore, IQ differences were unlikely to explain the findings.

TABLE 7.4. Regions of Differential Brain Activation during Failed Stop versus Go Response Trials for 22 Young People Exposed to Childhood Abuse, 17 Psychiatric Controls and 27 Healthy Controls

Comparison and Brain Region	BA	Cluster Level		Peak MNI Coordinates	Voxel Level
		No. of Voxels	<i>p</i> (corr.)		<i>Z</i>
Childhood Abuse > Healthy Controls					
Bilateral pre-SMA/SMA/dorsal ACC/superior frontal/precentral gyri/paracentral lobules Right postcentral/middle frontal gyri	24/32/6/4	3296	0.003	4,-6,72	4.76
				20,-4,74	4.19
				-8,2,74	4.09
Childhood Abuse > Psychiatric Controls					
Bilateral SMA	6	391	0.83	-2,-4,74	4.56

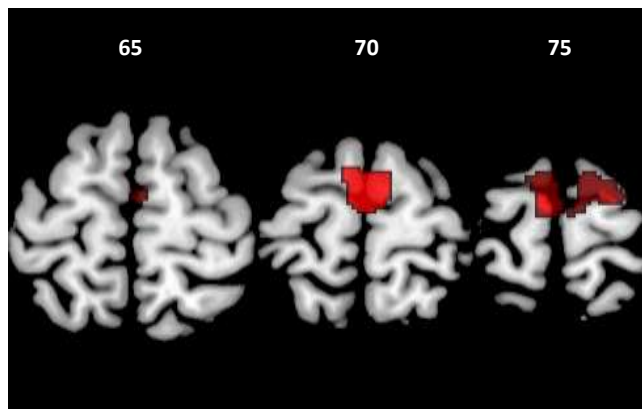
Abbreviations: MNI= Montreal Neurological Institute; corr=FWE-corrected; BA=Brodmann's Area; SMA=Supplementary motor area; ACC=Anterior cingulate cortex

FIGURE 7.3. Brain Activation during Failed Stop versus Successful Go Response Trials in Participants Exposed to Childhood Abuse compared to Healthy Controls



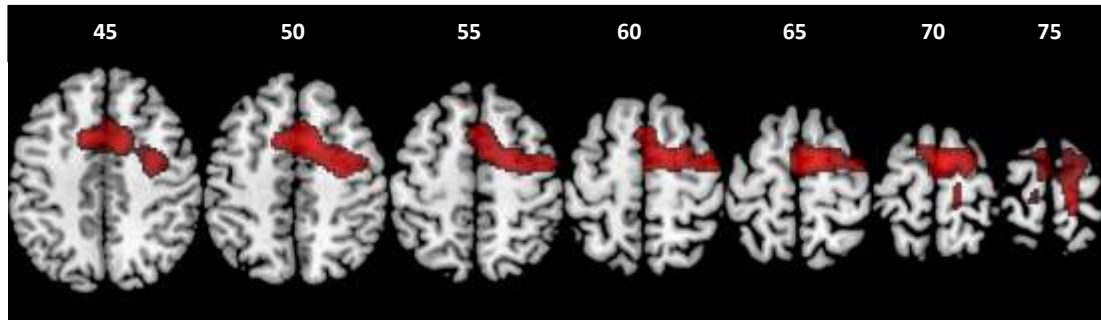
Axial sections showing increased brain activation to stop errors relative to successful go trials in 22 participants exposed to childhood abuse compared to 27 healthy controls, $p < 0.05$ FWE-corrected at the cluster-level. Axial slices are marked with the z coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

FIGURE 7.4. Brain Activation during Failed Stop versus Successful Go Response Trials in Participants Exposed to Childhood Abuse compared to Psychiatric Controls



Axial sections showing increased brain activation to stop errors relative to successful go trials in 22 participants exposed to childhood abuse compared to 17 psychiatric controls in some voxels within the bilateral SMA, $p < 0.05$ FWE-corrected at the voxel-level. Axial slices are marked with the z coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

FIGURE 7.5. Brain Activation during Failed Stop versus Successful Go Response Trials in Participants Exposed to Childhood Abuse compared to Healthy Controls with IQ as a Covariate



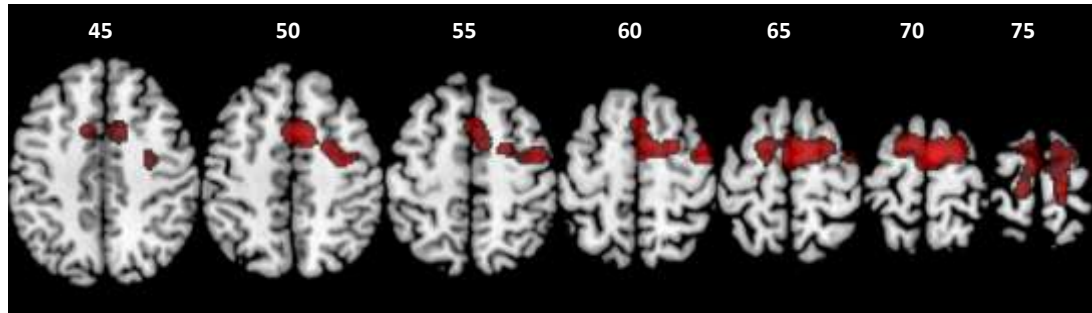
Axial sections showing increased brain activation to stop errors relative to successful go trials in 22 participants exposed to childhood abuse compared to 27 healthy controls with IQ as a covariate, $p < 0.05$ FWE-corrected at cluster level. Axial slices are marked with the z coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

Since the participants who had experienced abuse responded slower on go trials than healthy controls, data were re-analysed on a subsample (22 individuals exposed to abuse and 23 healthy controls) matched on mean go reaction time. The main findings remained significant (Figure 7.6). There were also no significant group differences between healthy individuals with high versus low mean go reaction time (median split at 475ms). Moreover, the main findings also remained significant when both go and post-error reaction times were included as covariates (Figure 7.7). Thus, performance differences were unlikely to confound the findings.

Successful Stop-Go Contrast

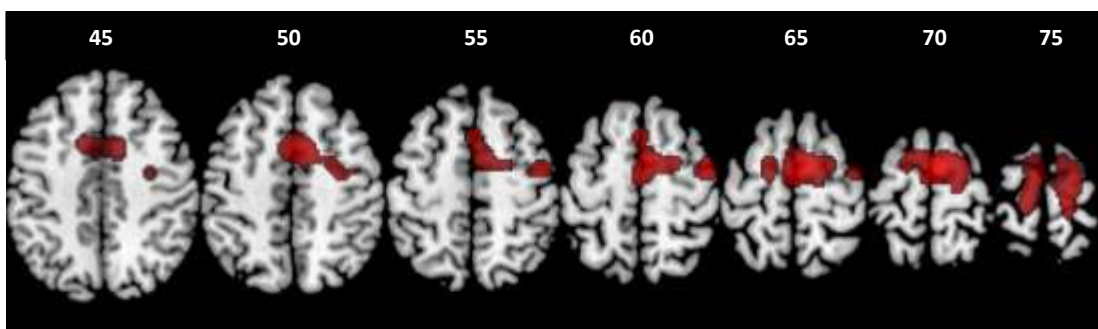
For successful inhibition, there were no significant group differences in activation (please see Table 7.5 & Figure 7.8 for within-group activations).

FIGURE 7.6. Brain Activation during Failed Stop versus Successful Go Response Trials in a Subsample of Participants Exposed to Childhood Abuse and Healthy Controls matched on Go Signal Reaction Times



Axial sections showing increased brain activation to stop errors relative to successful go trials in a subsample of 22 participants exposed to childhood abuse compared to 23 healthy controls matched on go signal reaction times, $p < 0.05$ FWE-corrected at cluster level. Axial slices are marked with the z coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

FIGURE 7.7. Brain Activation during Failed Stop versus Successful Go Response Trials in Participants Exposed to Childhood Abuse compared to Healthy Controls with Post-Error and Go Reaction Times as Covariates



Axial sections showing increased brain activation to stop errors relative to successful go trials in 22 participants exposed to childhood abuse compared to 27 healthy controls with post-error and go signal reaction times as covariates, $p < 0.05$ FWE-corrected at cluster level. Axial slices are marked with the z coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

TABLE 7.5. Regions of Brain Activation during Successful Stop versus Go Response Trials for 22 Young People Exposed to Childhood Abuse, 17 Psychiatric Controls and 27 Healthy Controls

Brain Region	BA	Cluster Level		Peak MNI Coordinates	Voxel Level
		No. of Voxels	<i>p</i> (corr.)		Z
<u>Healthy Controls</u>					
Right inferior/middle/superior frontal/ superior temporal gyri	47/10/46/9/8/21/22/20/19	22535	<0.0001	52,-60,12	6.45
Bilateral inferior/middle temporal/parahippocampal /	/37/39/36/35/30/4/6/3/1/2			38,46,30	6.37
hippocampus/thalamus gyri	/7/40/19/18			48,-76,10	6.28
Right pre-and postcentral gyri/precuneus					
Bilateral supramarginal/angular/inferior/superior parietal/					
cuneus/inferior/middle occipital/ lingual/fusiform gyri/					
cerebellum					
Right inferior frontal/superior temporal gyri/anterior insula	47/38/12	782	0.015	46,18,-14	5.35
				40,14,-10	5.48
				36,-4,-10	3.35
Left inferior frontal/middle/superior temporal gyri	47/21/38	534	0.045	-40,16,-8	4.99
				-50,2,-22	3.75
				-46,16,-22	3.56

Childhood Abuse

Bilateral inferior/middle/medial/superior frontal gyri/ anterior cingulate cortex / pre-and postcentral/inferior/middle/superior temporal/ inferior/superior parietal/angular/supramarginal/inferior / middle occipital/fusiform gyri/cuneus/ precuneus/ cerebellum	46/44/10/9/8/6/32/4/2/1/3 /20/37/19/21/39/22/42/40 /7/18	26497	<0.0001	-34,52,24 40,-50,-24 -44,-50,-24	6.26 5.94 5.87
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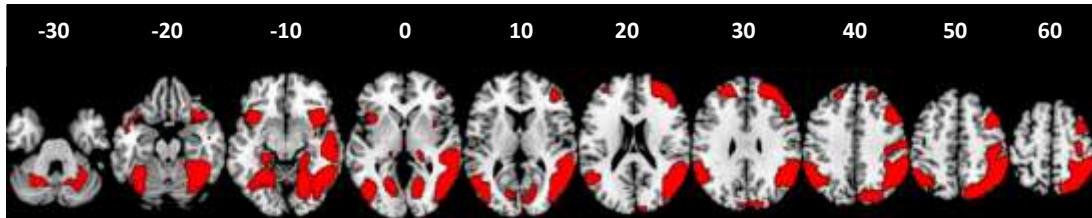
Psychiatric Controls

Right inferior/middle temporal /middle occipital /fusiform gyri	37/19/21/22/39/18/20	1281	0.002	58,-38,-6 50,-72,12 52,-46,-16	4.99 4.32 4.26
Left inferior/superior parietal lobules	40/7	972	0.007	-34,-44,42 -36,-46,50 -34,-52,62	4.57 4.51 4.21
Right supramarginal gyrus/inferior/superior parietal lobules	40/19/7	811	0.013	32,-68,50 36,-46,38 44,-54,46	3.77 3.65 3.62

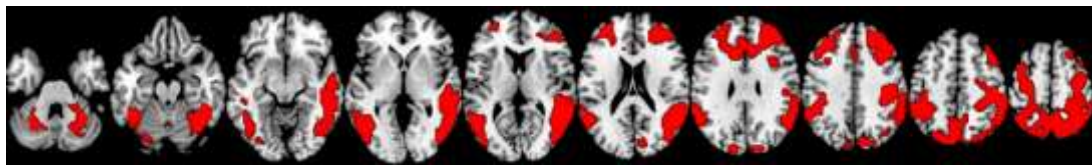
Abbreviations: MNI= Montreal Neurological Institute; corr=FWE-corrected; BA=Brodmann's Area

FIGURE 7.8. Brain Activation during Successful Stop versus Go Response Trials

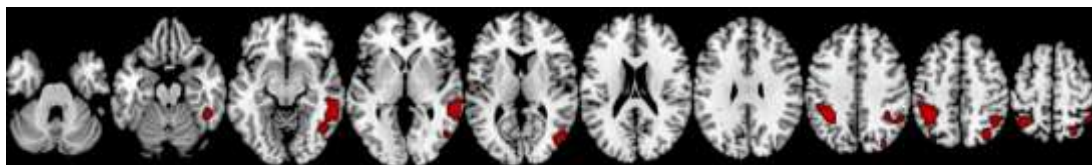
1) Healthy Controls



2) Childhood Abuse



3) Psychiatric Controls



Axial sections of brain activation during successful stop versus go response trials for 1) healthy controls, 2) participants exposed to childhood abuse and 3) psychiatric controls, $p < 0.05$, FWE-corrected at cluster level. Axial slices are marked with the z coordinate as distance in millimeters from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

7.4. Discussion

To my knowledge, this is the first fMRI study that examined the association between severe childhood abuse and error-related brain activation in medication-naïve drug-free young people. Behaviourally, the participants who had experienced abuse had slower go and post-error reaction times than healthy controls, but no abnormalities in the key inhibition measure (SSRT). As hypothesized, the young people with a history of abuse, relative to healthy controls, exhibited significantly increased activation in typical error monitoring regions of the dorsomedial frontal cortex including bilateral pre-SMA/SMA, dorsal ACC and superior frontal gyri. Furthermore, a smaller cluster in the SMA was significantly more activated in the childhood abuse group than the psychiatric control group, who did not differ from healthy controls. No significant group differences in activation were observed during successful stop trials, suggesting that the functional abnormalities were specific to error processing. Furthermore, the main findings remained significant in additional analyses controlling for IQ and task performance.

Converging evidence suggests that the dorsomedial frontal cortex is important for cognitive control, especially error processing (Ridderinkhof et al., 2004). Meta-analyses show that the dorsomedial frontal cortex, including the dorsal ACC and pre-SMA/SMA, is implicated in the detection of response errors and negative feedback which serve as signals that engage regulatory process in the lateral PFC to implement performance adjustments (Ridderinkhof et al., 2004). The pre-SMA/SMA and ACC are typical regions of error processing and performance monitoring in healthy adults (Li et al., 2008; Rubia, 2013; Rubia et al., 2013; Rubia et al., 2003; Rubia et al., 2007; Sharp et al., 2010) and children (Rubia, 2013; Rubia

et al., 2011; Rubia et al., 2013; Rubia et al., 2007) on the same or similar fMRI stop paradigms.

The SMA, which rapidly evaluates successful and erroneous actions, is known to be extensively involved in the assessment of ongoing actions (Roger et al., 2010) and plays a leading role in the action- and error-monitoring system (Bonini et al., 2014). Importantly, the participants exposed to abuse had greater error-related activation in some voxels within the SMA cluster compared to their psychiatric counterparts, suggesting that the hyperactivation of this key error processing region may be specific to childhood abuse relative to psychiatric controls.

Participants who had experienced abuse demonstrated normal inhibitory capacity, which is consistent with previous performance findings (Carrion et al., 2008; Elton et al., 2013). There were no significant group differences in brain activation during response inhibition, consistent with the negative findings of a previous fMRI study that used the same stop-signal paradigm (Elton et al., 2013). Although the other two studies found impaired inhibitory activation, they used the go/no-go (Carrion et al., 2008) and stop-change (Mueller et al., 2010) tasks and recruited youths who experienced early deprivation (Mueller et al., 2010) and adolescents with PTSS and childhood trauma including sexual abuse and witnessing violence (Carrion et al., 2008), which were not included in this study. Hence, the findings are not directly comparable and future studies are needed to examine the integrity of inhibitory networks in youth exposed to different types of maltreatment.

The increased sensitivity to errors as expressed in the slower post-error reaction time and hypersensitive dorsomedial frontal activation in participants who had experienced abuse relative to age-matched non-maltreated controls could possibly be due to the constant need to monitor their actions to avoid potential painful mistakes. This hypothesis would be in line with evidence that environmental adversities such as punitive parental behaviour are associated with enhanced ERN in ERP studies, which is related to hypersensitivity to punishment, hypervigilance (Santesso et al., 2011) and typical comorbidities of childhood maltreatment such as depression and anxiety (Olvet and Hajcak, 2008). The findings may be the cognitive counterpart of evidence from the emotional domain that individuals with a history of childhood maltreatment avoid negative events such as threat (Pine et al., 2005) and exhibit heightened neural reactivity to threat-related faces (Dannlowski et al., 2012a; McCrory et al., 2011; McCrory et al., 2013). Thus, it is speculated that persistent harsh punishment experiences in childhood may have sensitized the child to errors and led to an overactive error monitoring system.

The strength of this study is that all participants were medication-naïve, drug-free and that the abuse experience was carefully assessed and corroborated by social service records. Also, a psychiatric control group was included to determine the specificity of abuse. However, it is unclear to what extent pubertal development, malnutrition and prenatal drug exposure may have influenced the findings. The SES measure is limited without information on parents' income and education; however, youth often have difficulties in reporting this information (Currie et al., 1997). Although childhood sexual abuse was excluded as it has been shown to differ in many aspects (Ackerman et al., 1998) including a distinctive effect on the

somatosensory cortex (Heim et al., 2013), it is unrealistic to separate physical abuse from typically co-occurring emotional abuse and neglect (Edwards et al., 2003; Trickett et al., 2011).

In summary, using medication-naïve, drug-free, carefully assessed age-matched groups of young people exposed to severe childhood abuse and psychiatric controls matched on psychiatric comorbidities, the participants exposed to abuse had greater error-related dorsomedial frontal activation particularly in SMA than non-maltreated controls during error trials but showed no abnormal inhibitory activation. Hence, young people who had experienced abuse may possibly develop a greater sensitivity to errors as a form of adaptation to an environment in which errors frequently predict the occurrence of abuse. These findings represent a first step towards the delineation of abuse-specific neurofunctional abnormalities such as hyperactive error processing, which hopefully may lead to the development of specific treatment strategies to help individuals exposed to childhood abuse.

CHAPTER 8

Brain Functional Abnormalities during Sustained Attention in Young People with a History of Severe Childhood Abuse

8.1. Introduction

There is increasing interest in understanding the effects of childhood adversities on the developing brain given evidence that early environmental factors can have a substantial influence on the emerging brain architecture and long-term health of the person (Shonkoff and Garner, 2012). Childhood maltreatment, including physical, sexual and emotional abuse and neglect is common in the United Kingdom with paediatric prevalence rates of 7-10% (NSPCC, 2011). Furthermore, childhood adversities are significantly associated with first onsets of various psychiatric disorders including mood, anxiety and PTSD (Green et al., 2010).

The psychopathological outcomes associated with childhood maltreatment may be mediated by the disruption of cognitive processes and their associated neural underpinnings (Bremner and Vermetten, 2001). Childhood maltreatment has been associated with many adverse cognitive consequences such as low IQ and academic performance along with impaired attention, inhibition, emotion and reward processing (Pechtel and Pizzagalli, 2011). Several studies have reported attention impairment in individuals who had experienced childhood maltreatment such as auditory (DePrince et al., 2009; Nolin and Ethier, 2007) and visual (Beers and De Bellis, 2002; Bucker et al., 2012; De Bellis et al., 2009; Nolin and Ethier, 2007; Pollak et al., 2010) attention deficits. Children with maltreatment-related PTSD have been shown to make more omission errors than healthy controls during sustained

attention (Beers and De Bellis, 2002). Institutionalized children also had difficulties sustaining attention which was furthermore related to longer institutional care (Loman et al., 2013; McDermott et al., 2013). In adults, childhood physical abuse and neglect have also been associated with sustained attention deficits (Gould et al., 2012). Additionally, population-based studies report significant associations between childhood maltreatment and ADHD-inattentive symptoms (Fuller-Thomson et al., 2014; Ouyang et al., 2008).

To date, however, no fMRI study has examined sustained attention in individuals exposed to childhood maltreatment. Cognitive fMRI studies have mostly focused on the related function of inhibition, where youths exposed to childhood abuse demonstrated increased activation in IFC (Carrion et al., 2008; Mueller et al., 2010). Adults with a history of childhood maltreatment had no brain activation abnormalities; however, but had decreased functional connectivity of IFC and dorsal ACC which was related to symptoms of impulsivity and inattention (Elton et al., 2013).

Sustained attention is a key executive function important for mature adult goal-directed behaviour thought to underpin “higher-level” attentional processes such as selective and divided attention as well as general cognitive ability (Sarter et al., 2001). Fronto-striato-thalamo-parietal and cerebellar brain regions that mediate sustained attention have been shown to be progressively more activated with increasing age between childhood and adulthood in fMRI studies (Murphy et al., 2014; Smith et al., 2011). Childhood maltreatment may hence interfere with the normal development of attention functions. Moreover, deficits in sustained attention

may underlie a number of cognitive abnormalities found in common psychiatric comorbidities of childhood maltreatment such as depression (Maalouf et al., 2011), PTSD (Beers and De Bellis, 2002) and ADHD (Willcutt et al., 2005).

Therefore, this study examined the association between severe childhood (physical) abuse and brain activation during sustained attention in medication-naïve, drug-free young people using a parametrically modulated vigilance task requiring target detection with a progressively increasing load of sustained attention. Sexual abuse was excluded as it has been associated with different behavioural, psychiatric (Ackerman et al., 1998) and brain structure consequences (Heim et al., 2013). To assess the specificity of the association with childhood abuse, a third group of psychiatric controls that matched the participants who had experienced abuse on psychiatric comorbidities was included. It is hypothesized that participants exposed to abuse, relative to both healthy and psychiatric controls, would have abnormally reduced activation in typical dorsal and ventral fronto-striato-thalamo-cerebellar sustained attention regions, in particular during higher loads of attention.

8.2. Method

8.2.1. Participants

Seventy (23 individuals who had experienced childhood abuse, 20 psychiatric controls, 27 healthy controls) right-handed, medication-naïve, drug-free and age-matched young people were initially assessed by a child psychiatrist using the Development and Well-Being Assessment (DAWBA) (Goodman et al., 2000) designed to generate ICD-10 and DSM-IV psychiatric diagnoses. The Strengths and Difficulties Questionnaires (SDQ) (Goodman and Scott, 1999) and Beck's

Depression Inventory (BDI) (Beck et al., 1988) were used to provide psychopathology symptom scores. IQ was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). The Childhood Trauma Questionnaire (CTQ) (Bernstein and Fink, 1998) was used to measure the severity of childhood physical, emotional and sexual abuse and neglect. Socioeconomic status (SES) was measured by two non-sensitive items from the Family Affluence Scale (FAS) (Currie et al., 1997) on housing tenure and room occupancy.

Twenty-three young people who had experienced severe childhood physical abuse before the age of 12 years old were recruited through social services and psychiatric clinics. They scored ≥ 13 on the CTQ physical abuse subscale and the abuse history was corroborated by social service records and the Childhood Experience of Care and Abuse (CECA) interview (Bifulco et al., 1994). Psychiatric comorbidities included PTSD, depression, anxiety, conduct disorder and phobia. Two participants were excluded due to motion artefacts, leaving a final sample of 21 participants.

Twenty psychiatric patients matched with the participants who had experienced abuse on psychiatric comorbidities but with no history of childhood maltreatment (scored < 8 for physical abuse, < 9 for emotional abuse, < 6 for sexual abuse, < 10 for emotional neglect, < 8 for physical neglect on the CTQ) were recruited through psychiatric clinics and social services. PTSD patients experienced non-abuse related trauma (e.g. bullying, lived in the Afghanistan during wartime, witnessed a murder, experienced a car accident or the death of a loved one). One participant was excluded due to motion artefacts, leaving a final sample of 19 patients.

Twenty-seven healthy controls with no history of psychiatric illness and childhood maltreatment (scored < 8 for physical abuse, < 9 for emotional abuse, < 6 for sexual abuse, < 10 for emotional neglect, < 8 for physical neglect on the CTQ) were recruited through advertisements in the same geographic areas of South London to ensure similar socioeconomic status.

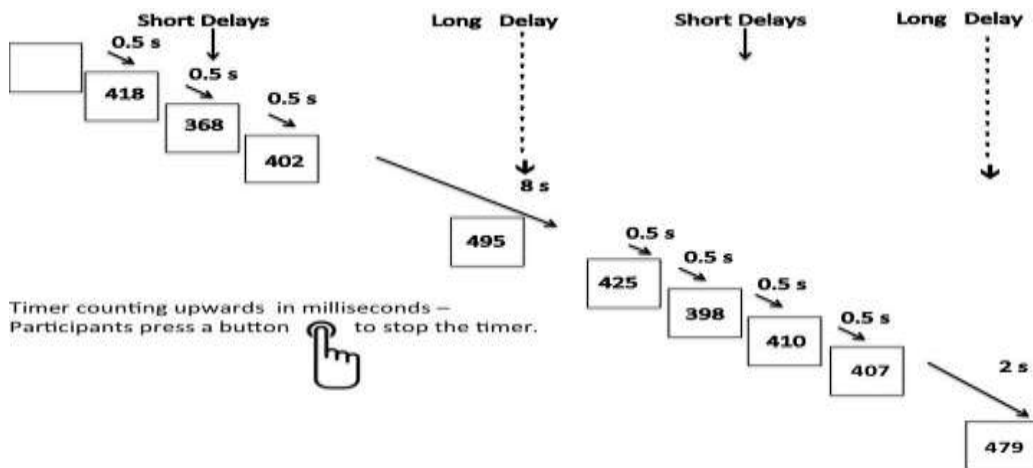
Exclusion criteria for all participants were childhood sexual abuse, learning disability, neurological abnormalities, epilepsy, drug abuse, IQ < 70 and the usual MRI contraindications. Urine tests were conducted using the 10 panel T-cup urine test (<http://www.testfield.co.uk>) to detect recent drug use. Participants' informed consent (and parental consent where age appropriate) and approval from the local Ethical Committee were obtained.

8.2.2. fMRI Paradigm: Sustained Attention Task (SAT)

Participants practiced the task once prior to scanning. The 12-min sustained attention task is a variant of psychomotor vigilance and delay tasks (Christakou et al., 2013; Murphy et al., 2014). Participants need to respond as quickly as possible to the appearance of a visual timer counting up in milliseconds via a right hand button response within 1s. The visual stimuli appear either after short, predictable consecutive delays of 0.5s, in series of 3-5 stimuli (260 in total) or after unpredictable time delays of 2s, 5s or 8s (20 each), pseudo-randomly interspersed into the blocks of 3-5 0.5s delays. The long, infrequent, unpredictable delays place a higher load on sustained attention/vigilance while the short, predictable 0.5s delays are typically anticipated (Miyake et al., 2004) placing a higher demand on

sensorimotor synchronization (Christakou et al., 2013; Murphy et al., 2014; Rubia et al., 1998) (Figure 8.1).

FIGURE 8.1. Schematic Presentation of the Sustained Attention Task (SAT)



Participants are required to press a right-hand button as soon as they see a timer appear on the screen counting seconds. The counter appears after either predictable short delays of 0.5s in blocks of 3-5 stimuli, or after unpredictable long delays of 2s, 5s or 8s, pseudo randomly interspersed into the blocks of 0.5s delays. The long second delays have a progressively higher load on sustained attention than the short 0.5s delays that are typically anticipated and have a higher load on sensorimotor synchronization.

8.2.3. Performance Data Analysis

Multiple repeated-measures ANOVAs with group as independent and delay as repeated measures were conducted to test for group differences in performance across the three long delays (2s, 5s, 8s) and a separate ANOVA for group differences for the short delay (0.5s) was conducted using SPSS 16 in the following measures: mean reaction time, intrasubject standard deviation of mean reaction time (SD_{intrasubject}), omission and premature errors. *P* values were Bonferroni-adjusted for multiple comparisons.

8.2.4. fMRI Image Acquisition

Gradient echo echo-planar MR imaging (EPI) data were acquired on a 3T GE Signa HDx system at the Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London. Stimulus images were projected on a screen, clearly visible through prism placed in front of participants' eyes. The body coil was used for RF transmission and an 8-channel head coil for RF reception. During the 12-minute run of the task, in each of 23 non-contiguous planes parallel to the anterior-posterior commissural, 480 T₂*-weighted MR images depicting BOLD contrast covering the whole brain were acquired with: echo time (TE) = 30ms, repetition time (TR) = 1.5s, 23 slices, flip angle = 70°, in-plane resolution = 3.75mm², field of view (FOV) = 240mm, slice thickness/gap = 5/0.5mm, matrix = 64 x 64. A high-resolution gradient EPI was also acquired for accurate spatial normalization (TE = 30ms, TR = 3s, 43 slices, flip angle = 90°, in-plane resolution = 1.875mm², FOV = 240mm, slice thickness/gap = 3/0.3mm, matrix = 128 x 128).

8.2.5. fMRI Image Analysis

Image preprocessing and whole-brain analyses were carried out using Statistical Parametric Mapping software (SPM8, www.fil.ion.ucl.ac.uk/spm). Data were realigned to correct for subject movement and co-registered to the high-resolution gradient EPI, which was then used to estimate the parameters for spatially normalizing the data into a standard anatomical space (Montreal Neurological Institute). The resulting normalized volume time series was spatially smoothed using a Gaussian kernel of 8-mm full width at half maximum.

Data were analysed within the framework of the general linear model. A single-subject (first-level) model was created for each participant, including regressors encoding each experimental condition (i.e., long delays of 2s, 5s and 8s, each contrasted with the implicit baseline of 0.5s delay). Movement parameters from the realignment procedure and premature and omission errors were included in the model as regressors of no interest. Next, contrast images from the first-level analyses were used to conduct flexible factorial whole-brain analyses at the group-level to examine the group by delay interaction effects. BOLD responses of the significant clusters were then extracted using MARSBAR and a 3 x 3 mixed ANOVA followed by post-hoc *t*-tests (correcting for multiple comparisons) was conducted using SPSS 18 to elucidate between-group differences. Given the limited studies aimed at specifying brain differences in childhood abuse populations, and to control for the false positive rate (using $p < 0.05$ FWE-corrected cluster statistics) while limiting potential Type II errors, an a-priori cluster-forming threshold of $p < 0.01$ for significant between-group differences was chosen.

Finally, correlational analyses were performed between the significant clusters and performance measures within each group and with abuse measures within the group of participants who had experienced abuse only.

8.3. Results

8.3.1. Participants Characteristics

The groups did not differ significantly in age, gender, ethnicity or SES, but did differ in IQ, as expected (Table 8.1). Since lower IQ is associated with childhood maltreatment (De Bellis et al., 2009; Nolin and Ethier, 2007), artificially matching groups on IQ is considered inappropriate as it creates unrepresentative groups

(Dennis et al., 2009). Also, covarying for IQ when groups are not randomly selected and the covariate is a pre-existing group difference that did not occur by chance violates ANCOVA assumptions (Dennis et al., 2009; Miller and Chapman, 2001). The primary data analyses are therefore presented without matching or covarying for IQ. However, to rule out any potential influence of IQ, additional confirmatory analyses on a subsample of IQ-matched participants and correlational analyses of IQ with brain activations in significant clusters and performance measures within each group were also conducted.

Although the study selected participants exposed to severe childhood physical abuse, they also experienced marked/severe childhood emotional abuse and neglect (Table 8.1) which typically co-occur with physical abuse, and hence are a representative group of the population with childhood abuse (Edwards et al., 2003; Trickett et al., 2011).

Healthy controls scored significantly lower on BDI ($p < 0.01$) and all SDQ difficulties subscales ($p < 0.001$) than the participants exposed to abuse, and on BDI ($p < 0.001$), SDQ emotional problems ($p < 0.001$) and hyperactivity ($p < 0.05$) subscales than psychiatric controls. The participants who had experienced abuse scored significantly higher than psychiatric controls on SDQ conduct ($p < 0.01$) and peer problems ($p < 0.05$) but lower on prosocial ($p < 0.01$) subscales (Table 8.1).

TABLE 8.1. Demographic Characteristic of 21 Young People Exposed to Childhood Abuse, 19 Psychiatric Controls and 27 Healthy Controls

	Childhood Abuse (N=21)		Psychiatric Controls (N= 19)		Healthy Controls (N=27)		Analysis		Between Groups
	Mean	SD	Mean	SD	Mean	SD	F(2, 64)	p (corr.)	
Age (years) [age range:13-20]	17.5	2.32	16.9	2.48	17.5	1.63	0.58	0.56	-
Socioeconomic status	2.77	0.69	2.94	0.66	3.22	0.75	2.53	0.09	-
IQ	90.0	12.6	93.6	13.0	105.4	10.1	11.3	0.001	CA, PC < HC
SDQ:									
<i>Emotional problems</i>	4.62	2.77	4.95	2.95	1.92	1.61	10.5	<0.001	CA, PC > HC
<i>Conduct problems</i>	4.43	2.01	2.37	2.36	1.68	1.60	11.5	<0.001	CA > PC, HC
<i>Hyperactivity</i>	5.38	2.40	4.68	2.65	2.84	2.14	7.08	0.002	CA, PC > HC
<i>Peer problems</i>	3.81	1.54	2.37	2.03	1.16	1.72	12.9	<0.001	CA > PC, HC
<i>Prosocial</i>	7.24	1.70	8.63	1.64	8.08	1.41	3.99	0.02	CA < PC
<i>Total difficulties score</i>	18.2	6.20	14.4	6.34	7.60	5.73	18.2	<0.001	CA, PC > HC
Beck's Depression Inventory	16.0	10.6	21.1	12.1	5.92	6.09	8.32	< 0.001	CA, PC > HC
CTQ:									
<i>Physical abuse</i>	20.8	5.04	6.21	1.58	5.52	0.94	117.4	<0.001	CA > PC, HC
<i>Emotional abuse</i>	18.0	4.40	7.11	1.79	6.04	1.13	94.4	<0.001	CA > PC, HC
<i>Sexual abuse</i>	5.14	0.65	5.39	0.78	5.11	0.42	1.18	0.31	-
<i>Physical neglect</i>	14.0	5.02	6.74	2.26	5.59	1.22	36.9	<0.001	CA > PC, HC

<i>Emotional neglect</i>	18.3	3.93	8.79	3.69	7.93	3.35	50.7	<0.001	CA > PC, HC
Age at onset of (physical) abuse (years)	4.24	2.55							
Duration of (physical) abuse (years)	8.29	3.20							
	N	%	N	%	N	%	χ^2	<i>p</i>	Between Groups
Gender (Males)	15	71	9	47	21	77	4.93	0.09	-
Ethnicity:							8.15	0.09	-
<i>Caucasian</i>	10	48	3	16	13	48			
<i>Afro-Caribbean</i>	8	38	10	52	12	44			
<i>Others (Asian/mixed)</i>	3	14	6	31	2	8			
Psychiatric diagnosis:									
<i>PTSD</i>	12	57	13	68	-				
<i>Depression</i>	6	29	6	31	-				
<i>Anxiety disorders</i>	4	19	5	26	-				
<i>Social phobia</i>	1	5	1	5	-				
<i>ADHD</i>	1	5	1	5					
<i>ODD/CD/Other disruptive behaviors</i>	4	19	3	16					

Abbreviations: CA=Childhood Abuse; PC=Psychiatric Controls; HC=Healthy Controls; corr=Bonferroi corrected; CTQ=Childhood Trauma Questionnaire; SDQ=Strength and Difficulties Questionnaire; ADHD=Attention Deficit Hyperactivity Disorder; PTSD=Post-Traumatic Stress Disorder; ODD=Oppositional Defiant Disorder; CD=Conduct Disorder

8.3.2. Task Performance

Paralleling the fMRI analyses where the 0.5s periods were analysed as implicit baseline, and the long delay periods were the targets of interest tapping into vigilance, the long delays were analysed separately from the short delay periods to assess the effects of delay, group and delay by group interactions (Table 8.2). There was no significant effect of delay across the three long delay periods. There was a significant group effect on omission ($F(2, 64) = 3.16, p < 0.05$) and premature errors ($F(2, 64) = 3.51, p < 0.05$) due to the participants who had experienced abuse and psychiatric controls making more errors than healthy controls ($p < 0.05$); without differing from each other. The group by delay interaction effect was significant at trend-levels for omission ($F(2, 64) = 2.44, p = 0.09$) and premature errors ($F(2, 64) = 2.46, p = 0.09$), due to the participants with a history of abuse making more omission errors in the 8s delay ($p < 0.05$), as well as both groups of psychiatric controls and participants who had experienced abuse making more premature errors in the 2s and 5s delays compared to healthy controls ($p < 0.05$).

For the 0.5s delay, there was a significant group effect on SDintrasubject ($F(2, 64) = 9.38, p < 0.001$) due to greater intrasubject variability in participants exposed to abuse and psychiatric controls relative to healthy controls ($p < 0.05$); as well as on omission errors ($F(2, 64) = 3.45, p < 0.05$) and at a trend-level on premature errors ($F(2, 64) = 2.89, p = 0.06$), due to the participants with a history of abuse making more errors in both measures than healthy controls ($p < 0.05$) (Table 8.3).

TABLE 8.2. Performance Measures for the Sustained Attention Task during 2s, 5s and 8s Delays for 21 Young People Exposed to Childhood Abuse, 19 Psychiatric Controls and 27 Healthy Controls

		Childhood Abuse (N=21)		Psychiatric Controls (N= 19)		Healthy Controls (N=27)	
	Delay	Mean	SD	Mean	SD	Mean	SD
MRT	2s	446	64	418	51	411	59
	5s	450	78	428	83	414	74
	8s	449	87	420	65	408	80
SDintrasubject	2s	101	50	71	31	74	38
	5s	93	50	74	46	85	61
	8s	84	43	83	45	77	43
Omission errors	2s	0.33	0.73	0.58	0.96	0.11	0.42
	5s	0.57	0.93	0.37	0.60	0.19	0.48
	8s	0.62	1.20	0.58	1.17	0.04	0.19
Premature errors	2s	6.43	3.93	6.16	3.01	4.00	3.16
	5s	7.38	4.65	6.84	3.39	4.30	3.74
	8s	6.95	4.23	6.53	3.52	5.15	3.92

Abbreviations: MRT=Mean Reaction Time (in ms); SDintrasubject=intrasubject variability of response of reaction time (in ms)

TABLE 8.3. Performance Measures for the Sustained Attention Task during 0.5s Delay for 21 Young People Exposed to Childhood abuse, 19 Psychiatric Controls and 27 Healthy Controls

	Childhood Abuse (N=21)		Psychiatric Controls (N= 19)		Healthy Controls (N=27)	
	Mean	SD	Mean	SD	Mean	SD
MRT	343	86	304	67	320	81
SDintrasubject	115	35	100	19	78	32
Omission errors	8.33	15.5	3.84	7.73	1.00	1.44
Premature errors	20.5	16.7	10.5	9.67	9.70	19.8

Abbreviations: MRT=Mean Reaction Time (in ms); SDintrasubject=intrasubject variability of response of reaction time (in ms)

8.3.3. Brain Activation

Motion

MANOVAs showed no significant group differences in maximum translation ($F(6,124) = 1.67, p > 0.05$) or maximum rotation ($F(6,124) = 1.09, p > 0.05$) parameters.

Group/Delay Effect

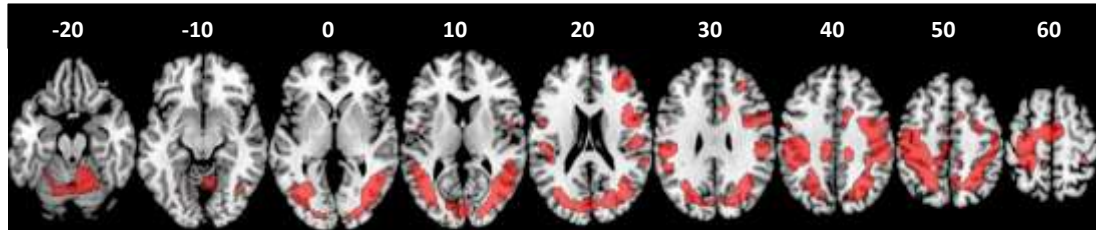
There were no significant group differences across all delays (please see Figures 8.2-8.4 for brain activations within each group and Figure 8.5 for main effect of delay).

Group by Delay Interaction Effects

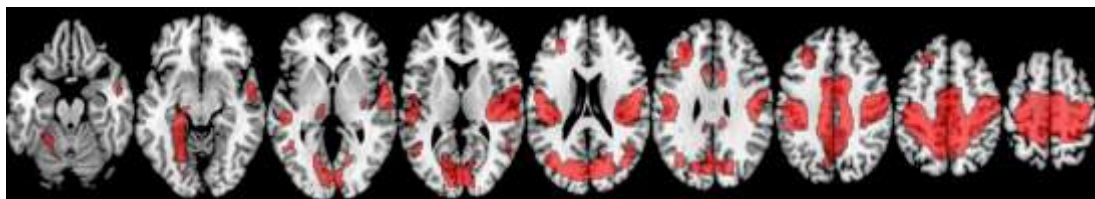
There was a significant group by delay interaction effect in three large clusters: cluster 1 comprised left-hemispheric IFC, middle, superior frontal and precentral gyri, pre-SMA/SMA and anterior insula; cluster 2 was a large midline cluster extending from ACC to caudate, putamen, thalamus, PCC, cuneus, precuneus, lingual gyri, to cerebellar vermis, right parahippocampal gyrus and hippocampus; cluster 3 comprised left inferior, middle and superior temporal gyri, inferior and middle occipital gyri, fusiform gyrus and cerebellum. Post-hoc analyses at each delay showed that the participants with a history of abuse had significantly lower activation during the longest delay only compared to healthy controls in clusters 1 ($p < 0.05$) and 2 ($p < 0.01$) and at a trend-level ($p < 0.06$) in cluster 3 but did not differ from psychiatric controls. In cluster 3, psychiatric controls had lower activation compared to the participants who had experienced abuse in the 2s delay ($p < 0.05$) and compared to healthy controls in the 5s delay ($p < 0.05$) (Table 8.4, Figure 8.6).

FIGURE 8.2. Brain Activation during 1) 2s, 2) 5s and 3) 8s Delays in Healthy Controls

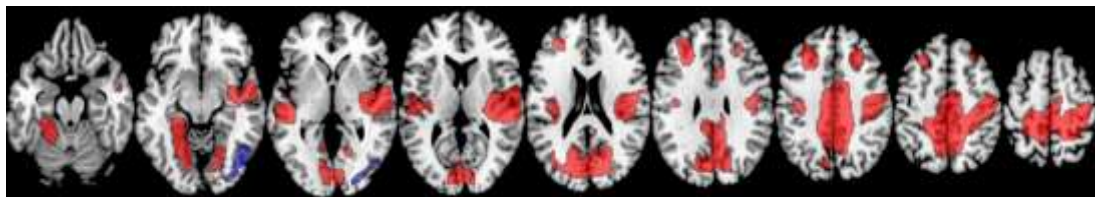
1) 2s Delay



2) 5s Delay



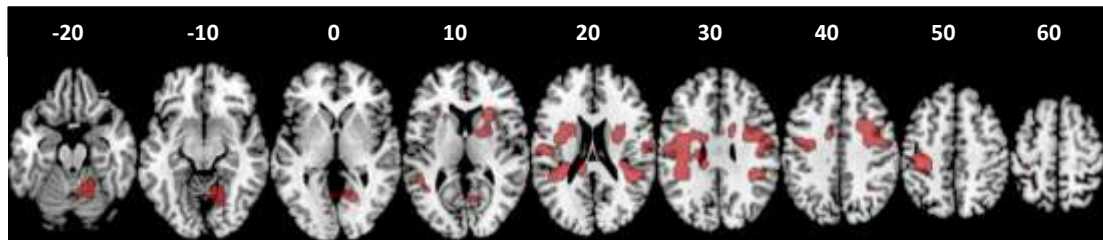
3) 8s Delay



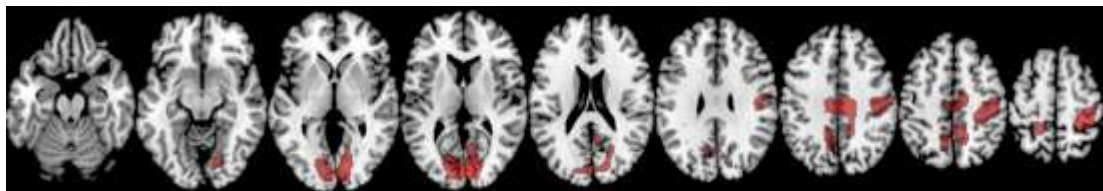
Axial sections of brain activation (Red) and deactivation (Blue) during 2s, 5s and 8s delays in healthy controls, $p < 0.05$, FWE-corrected at cluster level. Axial slices are marked with the z coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

FIGURE 8.3. Brain Activation during 1) 2s, 2) 5s and 3) 8s Delays in Young People Exposed to Childhood Abuse

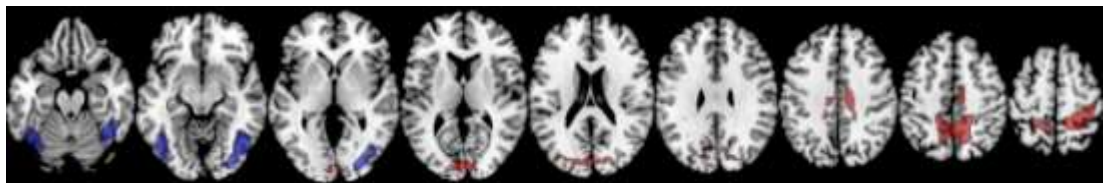
1) 2s Delay



2) 5s Delay



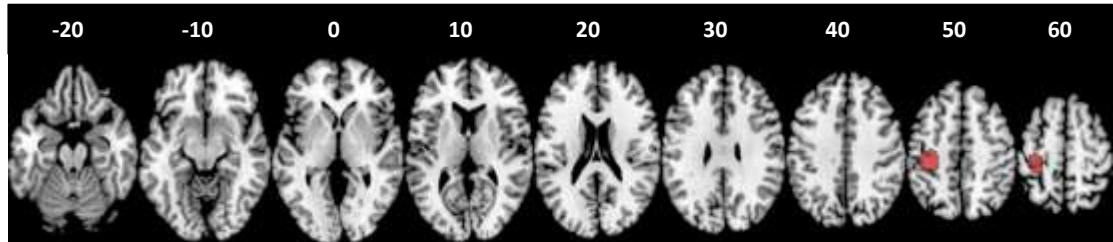
3) 8s Delay



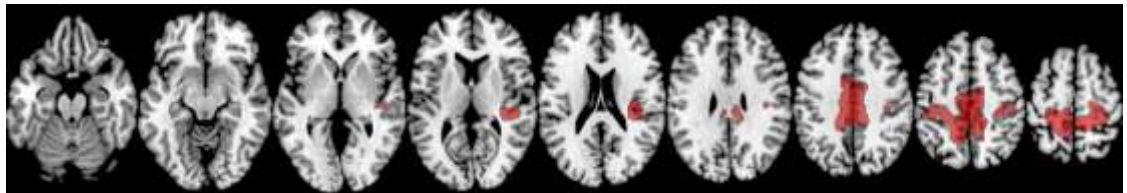
Axial sections of brain activation (Red) and deactivation (Blue) during 2s, 5s and 8s delays in young people who had experienced childhood abuse, $p < 0.05$, FWE-corrected at cluster level. Axial slices are marked with the z coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

FIGURE 8.4. Brain Activation during 1) 2s, 2) 5s and 3) 8s Delays in Psychiatric Controls

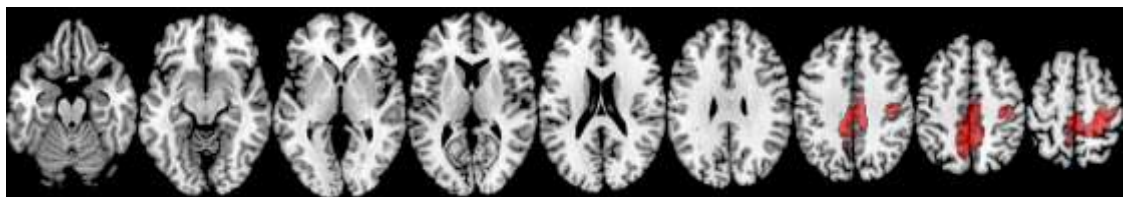
1) 2s Delay



2) 5s Delay

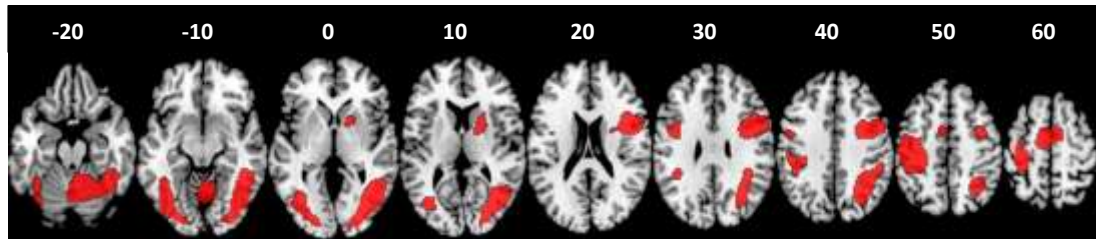


3) 8s Delay



Axial sections of brain activation during 2s, 5s and 8s delays in psychiatric controls, $p < 0.05$, FWE-corrected at cluster level. Axial slices are marked with the z coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

FIGURE 8.5. Main Effect of Delay on Brain Activation during Sustained Attention in Young People Exposed to Childhood Abuse, Psychiatric Controls and Healthy Controls



Axial sections showing main effect of delay on brain activation during sustained attention across 21 young people who had experienced childhood abuse, 19 psychiatric controls and 27 healthy controls, as revealed by F test, $p < 0.05$, FWE-corrected at cluster level. Axial slices are marked with the z coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

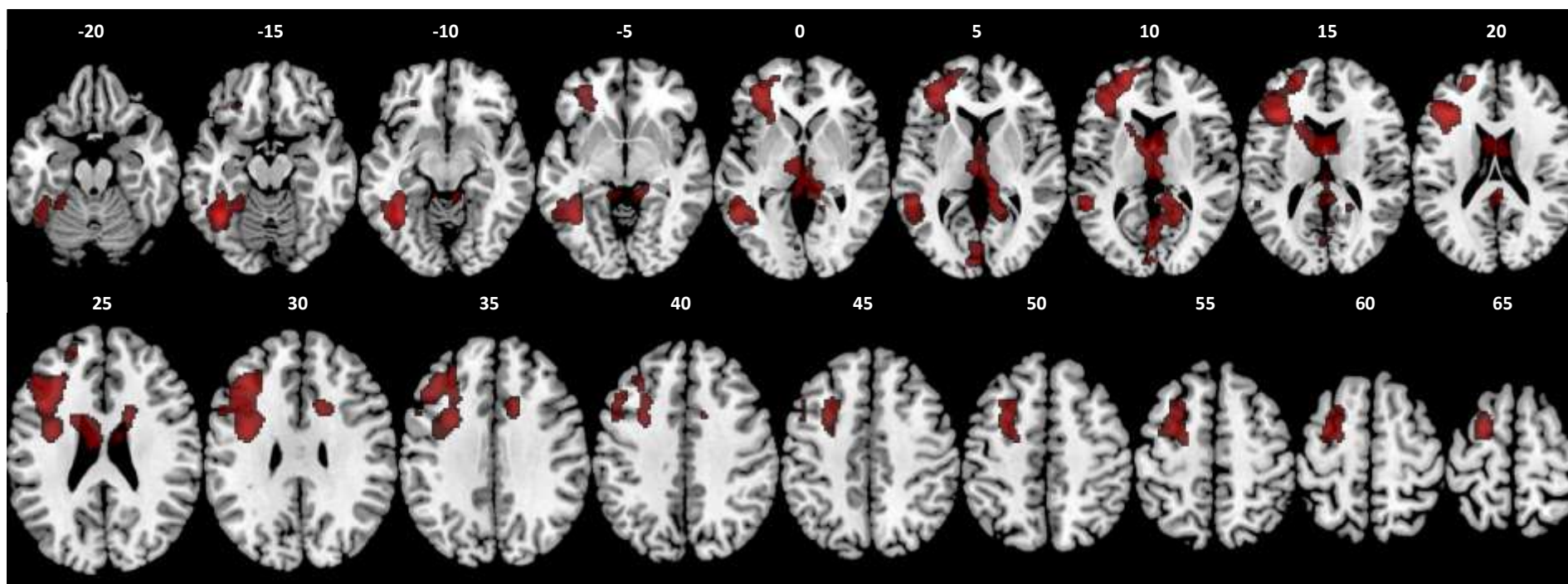
TABLE 8.4. ANOVA Group by Delay Interaction Effect on Brain Activation between 21 Young People Exposed to Childhood Abuse, 19 Psychiatric Controls and 27 Healthy Controls

Brain Region	BA	Cluster Level		Peak MNI Coordinates	Subject Contrast		
		No. of Voxels	<i>p</i> (corr.)		2s	5s	8s
Cluster1: Left inferior/middle/superior frontal/ precentral gyri/pre-SMA/SMA/anterior insula	47/44/45/46/10/11/ 9/8/6/4	3974	<0.001	-38,26,16 -24,52,12 -36,-2,28	-	-	CA<HC
Cluster2: Bilateral ACC/ caudate/putamen/ thalamus/ PCC/cuneus/precuneus/ lingual gyri/anterior cerebellum/vermis right parahippocampal/hippocampus	23/30/31/29/17/18/ 7/27/35/19/24/32	3046	<0.001	4,2,14 -8,-8,26 16,-48,8	-	-	CA<HC
Cluster3: Left inferior/middle/superior temporal/ inferior/middle occipital/fusiform gyri/ parahippocampal gyrus/cerebellum	37/19/21/22/39/20/ 30/42	1989	0.001	-40,-54,-14 -54,-44,10 -40,-44,-10	PC<CA	PC<HC	CA<HC [#]

Abbreviations: ANOVA=Analysis of Variance; MNI= Montreal Neurological Institute; corr=FWE-corrected; BA=Brodmann's Area; CA=Childhood Abuse; PC=Psychiatric Controls; HC=Healthy Controls; SMA=Supplementary motor area; ACC=Anterior cingulate cortex; PCC=posterior cingulate cortex

[#] Significant at trend level $p=0.06$

FIGURE 8.6. Group by Delay Interaction Effect on Brain Activation during Sustained Attention in Young People Exposed to Childhood Abuse, Psychiatric Controls and Healthy Controls



Axial sections showing group by delay interaction effect on brain activation during sustained attention between 21 young people who had experienced childhood abuse, 19 psychiatric controls and 27 healthy controls as revealed by F test, $p < 0.05$, FWE-corrected at the cluster level. Axial slices are marked with the z coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

Given that the participants who had experienced abuse had significantly lower IQ than healthy controls, data were re-analysed using an IQ-matched subsample (19 individuals exposed to abuse, 19 psychiatric controls and 18 healthy controls) (Figure 8.7). All main findings remained significant. Also within each group, IQ did not significantly correlate with brain activation or with omission errors.

To further investigate the group by delay interaction effects, group differences in linear trend effects of delay on brain activation in each of the three clusters were examined. There was a significant linear trend of progressively decreasing activation in participants who had experienced abuse relative to healthy controls across the three delays in cluster 2 ($F(1, 46) = 4.57, p < 0.05$) and relative to psychiatric controls in clusters 1 ($F(1, 38) = 4.76, p < 0.05$), 2 ($F(1, 38) = 5.15, p < 0.05$) and 3 ($F(1, 38) = 7.22, p < 0.05$).

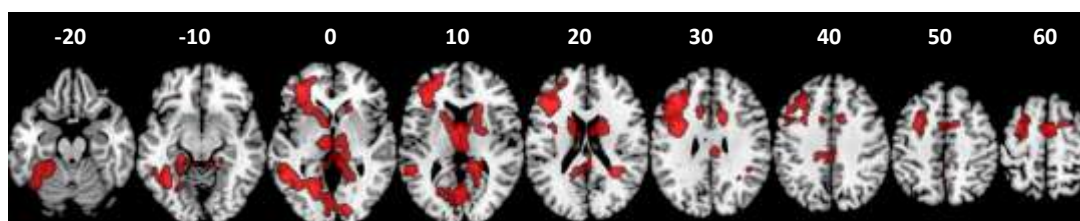
Correlational Analyses

To investigate whether the significant clusters were associated with abuse measures and the main performance measure of omission errors, BOLD responses in each cluster for the 8s delay --with the greatest group differences-- were extracted for each participant and correlated with omission errors within each group and with abuse measures within the group of participants who had experienced abuse only.

For healthy controls, omission errors were negatively correlated with activation in clusters 1 ($r = -0.7, p < 0.001$), 2 ($r = -0.5, p < 0.01$) and 3 ($r = -0.5, p < 0.01$). No significant correlations between omission errors and activation were observed in the participants with a history of abuse and psychiatric controls. For the

participants who had experienced abuse, omission errors correlated at a trend-level positively with abuse duration ($r = 0.42$, $p = 0.06$).

FIGURE 8.7. Group by Delay Interaction Effect on Brain Activation during Sustained Attention in a Subsample of Young People Exposed to Childhood Abuse, Psychiatric Controls and Healthy Controls matched on IQ



Axial sections showing group by delay interaction effect on brain activation during sustained attention in a subsample of 19 young people who had experienced childhood abuse, 19 psychiatric controls and 18 healthy controls matched on IQ, as revealed by F test, $p < 0.05$, FWE-corrected at the cluster level. Axial slices are marked with the z coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

8.4. Discussion

To my knowledge, this is the first fMRI study that examined the neurofunctional correlates of sustained attention in severe childhood abuse. In a parametrically designed sustained attention task, medication-naïve, drug-free young people who had experienced childhood abuse, compared to healthy controls, displayed lower activation during the longest delay only in typical dorsal and ventral sustained attention regions of left DLPFC and IFC, ACC/pre-SMA/SMA, bilateral striato-thalamic, cingulate and cerebellar areas. Furthermore, this was because the childhood abuse group showed a linear trend of progressively decreasing activation in these regions across the three delays/attention loads, which was specific relative to the psychiatric control group. Behaviourally, the participants who had experienced

abuse made more omission errors than healthy controls during the longest delays, which correlated positively, albeit at a trend-level, with the duration of abuse. Furthermore, the main findings remained significant in additional analysis controlling for IQ.

Young people who had experienced abuse showed activation deficits in frontal control regions important for sustained attention such as DLPFC, IFC/insula, pre-SMA/SMA and ACC (Christakou et al., 2013; Cubillo et al., 2012; Murphy et al., 2014; Rubia et al., 2009a; Rubia et al., 2009b; Smith et al., 2011; Tana et al., 2010; Voisin et al., 2006). The anterior insula, implicated in high-level cognitive control and attentional processes (Menon and Uddin, 2010), and the ACC form the core of a salience network that facilitates the detection of important environmental stimuli (Menon and Uddin, 2010; Seeley et al., 2007). The PCC, which is involved in maintaining a vigilant attentional state (Gilbert et al., 2007; Hahn et al., 2007), together with the hippocampus and insula form part of the paralimbic system and visuo-motor pathways essential for bottom-up visual-spatial attention processes (Gur et al., 2007; Mohanty et al., 2008). Therefore, the findings suggest a deficit in both top-down frontal executive attention control and bottom-up visual-spatial saliency processing in the participants who had experienced abuse relative to healthy controls during the most challenging attention condition. The deficits may possibly be related to the combination of abuse experience and psychiatric comorbidities as they were not observed in the psychiatric controls, who did not differ significantly from the healthy controls or participants with a history of abuse. Furthermore, although the activation deficits *per se* were not different between the participants who had experienced abuse and psychiatric controls, the linear trend findings of a

progressively deteriorating activation across all delays was specific to the participants exposed to abuse relative to the psychiatric controls. The findings suggest that the participants who had experienced abuse appear to exhibit progressively weaker brain activation with increasing delays and that this progressive deterioration is abuse-specific relative to psychiatric controls.

The findings also suggest that neurofunctional abnormalities during sustained attention in young people exposed to childhood abuse are intact in easier attention conditions and manifest only during the most challenging condition. This is interesting in view of neurofunctional deficits in the same task in people with ASD and ADHD (Christakou et al., 2013; Murphy et al., 2014) in all attention/delay conditions, suggesting less pervasive neurofunctional attention deficits in the young people with a history of abuse as they only manifest at the more challenging attention/delay conditions.

The human brain is a highly plastic organ that is continually modified by experience across development. Given that the DLPFC, IFC, striatum, ACC and cerebellum develop relatively late functionally by late adolescence (Rubia, 2013), they may be more susceptible to impairment following childhood adversities. Hence, functional abnormalities of these late developing DLPFC/IFC-cingulo-striatal-cerebellar regions during sustained attention may suggest an environmentally triggered disturbance in the normal development of these attention networks as a consequence of childhood abuse.

At the performance level, the participants who had experienced abuse made more premature and omission errors than healthy controls and the omission errors further correlated positively, albeit at a trend-level, with the duration of abuse. This is consistent with previous findings of more omission errors during sustained attention tasks in children with maltreatment-related PTSD (Beers and De Bellis, 2002) and in children with longer institutional care (Loman et al., 2013). Furthermore, the dorsal and ventral attention regions that had lower activation in the participants exposed to abuse were associated with better performance (less omission errors) in the healthy controls only, suggesting that in healthy individuals these regions are recruited to perform better with increasing vigilance loads; while poor performance in the participants who had experienced abuse may be due to poor recruitment of these regions.

The strength of this study is that all participants were medication-naïve, drug-free and that the abuse experience was carefully assessed and corroborated by social service records. Also, a psychiatric control group was included to determine the specificity of abuse. However, it is unclear to what extent pubertal development, malnutrition and prenatal drug exposure may have influenced the findings. The SES measure is limited without information on parents' income and education; however, youth often have difficulties in reporting this information (Currie et al., 1997). Although childhood sexual abuse was excluded as it has been shown to differ in many aspects (Ackerman et al., 1998) including distinctive effects on the somatosensory cortex (Heim et al., 2013), it is unrealistic to separate physical abuse from typically co-occurring emotional abuse and neglect (Edwards et al., 2003; Trickett et al., 2011).

In summary, using medication-naïve, drug-free, carefully assessed age-matched groups of young people exposed to severe childhood abuse and psychiatric controls matched on psychiatric comorbidities, the participants with a history of abuse had activation deficits in typical sustained attention regions of fronto-striato-thalamo-cerebellar areas compared to healthy controls during the longest delay condition. This appeared to be associated with a progressively diminishing activation in these regions with increasing delays, which was abuse-specific relative to the psychiatric controls. The findings represent a first step towards the delineation of abuse-related neurofunctional abnormalities in sustained attention, which may help in the development of effective treatment strategies for individuals who had experienced childhood abuse.

CHAPTER 9

Altered Neural Processing of Fearful and Neutral Facial Expressions in Young People with a History of Severe Childhood Abuse

9.1. Introduction

There is increasing interest in understanding the effects of early environmental adversities on the developing brain. Childhood maltreatment, including physical, sexual and emotional abuse and neglect is common in the United Kingdom with paediatric prevalence rates of 7-10% (NSPCC, 2011). Furthermore, childhood adversities are significantly associated with first onsets of various psychiatric disorders including mood, anxiety and PTSD (Green et al., 2010).

Facial expressions of emotion are important signals that guide social interactions. Children develop the ability to categorize facial expressions from a young age (Pollak and Kistler, 2002), which is invaluable for successful social interaction. Compared to non-maltreated peers, children exposed to maltreatment experience an atypical range of emotional cues, including less positive (Bugental et al., 1990) and more negative emotion (Herrenkohl et al., 1991). Altered emotion processing is consistently reported in individuals exposed to childhood maltreatment, with neglected children having emotion discrimination deficits (Pollak et al., 2000) and individuals who had been abused having differential processing of emotions that is more sensitive to anger and fear (Pollak et al., 2000; Pollak and Tolley-Schell, 2003; Pine et al., 2005; Masten et al., 2008; Gibb et al., 2009; Caldwell et al., 2014).

In addition, there is evidence of abnormally enhanced activation in the limbic regions of amygdala and hippocampus in response to negative facial expressions

(angry, fearful) in young people who had been abused (McCrory et al., 2011, 2013; Garrett et al., 2012) and institutionalized (Maheu et al., 2010; Tottenham et al., 2011) compared to healthy controls; where the enhanced amygdala activation to fearful faces was furthermore correlated with lower social competence and mediated the association between early rearing conditions and decreased eye-contact (Tottenham et al., 2011), while the enhanced amygdala activation to angry faces was positively correlated with the number of placements in foster care and negatively correlated with the time spent in the adoptive family (Maheu et al., 2010) and with age at onset of emotional maltreatment and neglect (McCrory et al., 2013). In adult studies, healthy adults with a history of childhood physical abuse had significantly greater activation in the left amygdala in response to angry and fearful faces than those without childhood abuse (Taylor et al., 2006). Childhood maltreatment in healthy adults was also strongly correlated with right amygdala responsiveness to fearful and angry faces (Dannlowski et al., 2012a).

Children who had been physically abused are at heightened risk for reactive aggression (Shields and Cicchetti, 1998) and it has been postulated that the perceptual systems used to recognize social signals, such as facial expressions, link early affective experience with the development of psychopathology. Individuals who had been physically abused are hypersensitive to negative facial expressions (Pollak et al., 1997, 2000, 2001; Pollak and Kistler, 2002; Pollak and Sinha, 2002; Pollak and Tolley-Shell, 2003), which may lead to altered brain activity and the perception of neutral facial expressions as negative as has been observed in patients with depression (Oliveira et al., 2013; Maniglio et al., 2014) and social anxiety disorder (Cooney et al., 2006).

Therefore, this study examined the association between severe childhood (physical) abuse and neural networks of emotion processing. Sexual abuse was excluded as it has different effects on brain structure (Heim et al., 2013) and different behavioural and psychiatric consequences (Ackerman et al., 1998). To assess the specificity of the association with childhood abuse, a third group of psychiatric controls that matched the participants who had experienced childhood abuse on psychiatric comorbidities was included. It is hypothesized that the young people exposed to abuse would have reduced activation in in fronto-limbic brain regions compared to healthy and psychiatric controls when processing negative emotional stimuli, particularly fear and anger.

9.2. Method

9.2.1. Participants

Seventy (23 individuals who had experienced childhood abuse, 20 psychiatric controls, 27 healthy controls) right-handed, medication-naïve, drug-free and age-matched young people were initially assessed by a child psychiatrist using the Development and Well-Being Assessment (DAWBA) (Goodman et al., 2000) designed to generate ICD-10 and DSM-IV psychiatric diagnoses. The Strengths and Difficulties Questionnaires (SDQ) (Goodman and Scott, 1999) and Beck's Depression Inventory (BDI) (Beck et al., 1988) were used to provide symptom scores on psychopathology. IQ was assessed using Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). The Childhood Trauma Questionnaire (CTQ) (Bernstein and Fink, 1998), a 25-item retrospective self-report questionnaire to measure the severity of childhood physical, sexual and emotional abuse, and physical and emotional neglect was administered. Each of the five subscales has a possible

range of 5 to 25. Socioeconomic status (SES) was measured by two non-sensitive items from the Family Affluence Scale (FAS) (Currie et al., 1997) on housing tenure and room occupancy.

Twenty-three young people who had experienced childhood physical abuse before the age of 12 years old were recruited through social services and psychiatric clinics. They scored ≥ 13 on the CTQ physical abuse subscale and the abuse history was corroborated by social service records and the Childhood Experience of Care and Abuse (CECA) interviews (Bifulco et al., 1994). Psychiatric comorbidities included PTSD, depression, anxiety, conduct disorder and phobia. Three participants were excluded due to motion artefacts, leaving a final sample of 20 participants.

Twenty psychiatric patients matched with the participants who had experienced abuse on psychiatric comorbidities but with no history of childhood maltreatment (scored < 8 for physical abuse, < 9 for emotional abuse, < 6 for sexual abuse, < 10 for emotional neglect, < 8 for physical neglect on the CTQ) were recruited through psychiatric clinics and social services. PTSD patients experienced non-abuse related trauma (e.g. bullying, lived in the Afghanistan during wartime, witnessed a murder, experienced a car accident or the death of a loved one).

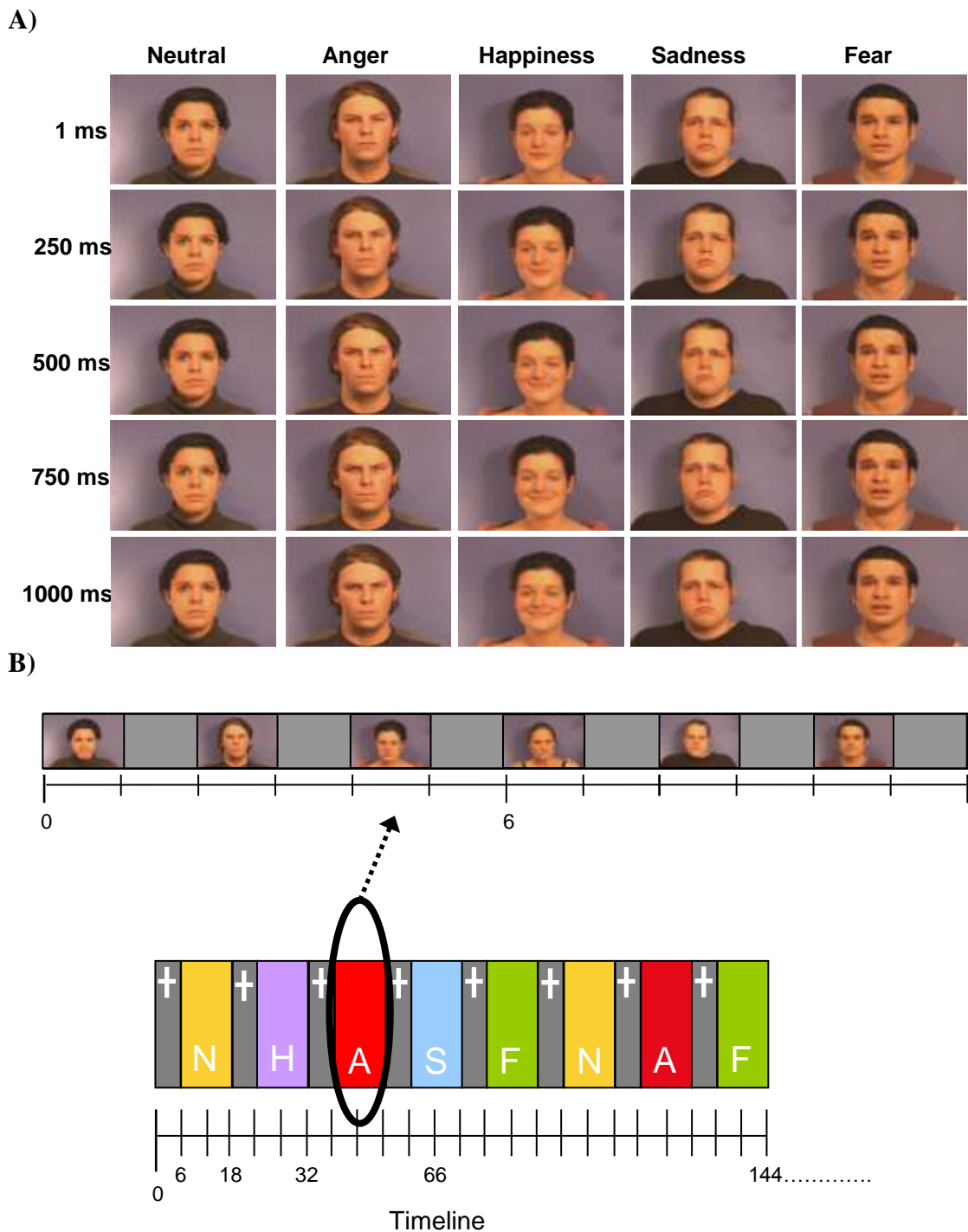
Twenty-seven healthy controls with no history of psychiatric illness and childhood maltreatment (scored < 8 for physical abuse, < 9 for emotional abuse, < 6 for sexual abuse, < 10 for emotional neglect, < 8 for physical neglect on the CTQ) were recruited through advertisements in the same geographic areas of South London to ensure similar socioeconomic background.

Exclusion criteria for all participants were childhood sexual abuse, learning disability, neurological abnormalities, epilepsy, drug abuse, $IQ < 70$, and the usual MRI contraindications. Urine tests were conducted using the 10 panel T-cup urine test (<http://www.testfield.co.uk>) to detect recent drug use. Participants' informed consent (and parental consent where age appropriate) and approval from the local Ethical Committee were obtained.

9.2.2. fMRI Paradigm: Emotion Processing Task (EPT)

Participants practiced the 8-minute block design fMRI emotion processing task, which measures the ability to recognize and discriminate between dynamic facial expressions of emotions, once prior to scanning. Participants were shown series of 1s video clips of 6 actors (3 males) displaying neutral, fearful, angry, sad or happy facial expressions (Figure 9.1). Clips were taken from a validated set of stimuli (Simon et al., 2008) and cut backward from the peak of the expression to avoid different lengths and variability of exposure. Blocks of stimuli (12s) of each of the 5 emotions were interspersed with a fixation cross baseline condition (6s). Each emotion was presented in a block of 6 of the 1s stimuli (each actor shown once, all the same emotion) with each stimuli followed by a 1s gap. Each emotion block was repeated 5 times in a pseudo-random order and the neutral condition was repeated 6 times. Participants were instructed to identify each clip as positive, neutral or negative by immediately pressing one of three buttons with the right index, middle and ring fingers, respectively.

FIGURE 9.1. Schematic Presentation of the Emotion Processing Task (EPT)



A) Examples of actors expressing the five emotions: neutral, anger, happiness, sadness and fear. Five time points in the clip (1, 250, 500, 750, 1000 ms) are displayed. B) Showing (top row) an example emotion block (angry) and (bottom row) the block structure of the task comprising 6s fixation cross blocks (+) interspersed with 12s emotion blocks (A= angry, F= fear, H= happy, N= neutral, S= sad)

9.2.3. Performance Data Analysis

For each emotion condition, mean percentage errors and reaction time were calculated for each of the three groups and MANOVAs were carried out to identify significant group differences. The errors for the neutral condition were broken down into negative errors (where neutral was perceived as negative) and positive errors (where neutral was perceived as positive) and *t*-tests were carried out to identify group differences.

9.2.4. fMRI Image Acquisition

Gradient echo echo-planar MR imaging (EPI) data were acquired on a 3T GE Signa HDx system at the Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London. Stimulus images were projected on a screen, clearly visible through prism placed in front of participants' eyes. The body coil was used for RF transmission and an 8-channel head coil for RF reception. During the 8-minute run of the task, in each of 23 non-contiguous planes parallel to the anterior-posterior commissural, 237 T₂*-weighted MR images depicting BOLD contrast covering the whole brain were acquired with: echo time (TE) = 30ms, repetition time (TR) = 2s, 23 slices, flip angle = 75°, in-plane resolution = 3.75mm², field of view (FOV) = 240mm, slice thickness/gap = 5/0.5mm, matrix = 64 x 64. A high-resolution gradient EPI was also acquired for accurate spatial normalization (TE = 30ms, TR = 3s, 43 slices, flip angle = 90°, in-plane resolution = 1.875mm², FOV = 240mm, slice thickness/gap = 3/0.3mm, matrix = 128 x 128).

9.2.5. fMRI Image Analysis

Image preprocessing and whole-brain analyses were carried out using Statistical Parametric Mapping software (SPM8, www.fil.ion.ucl.ac.uk/spm). Data were realigned to correct for subject movement and co-registered to the high-resolution gradient EPI, which was then used to estimate the parameters for spatially normalizing the data into a standard anatomical space (Montreal Neurological Institute). The resulting normalized volume time series was spatially smoothed using a Gaussian kernel of 8-mm full width at half maximum.

Data were analysed within the framework of the general linear model. A single-subject (first-level) model was created for each participant, including regressors encoding fixation, neutral, fearful, angry, sad and happy conditions to allow for contrasts of each emotion condition against the fixation baseline. Movement parameters from the realignment procedure were included in the model as regressors of no interest. For second-level (group) analyses, contrast images from the first-level analyses were used to conduct full factorial whole-brain analyses for each emotion condition. BOLD responses are reported using a stringent cluster threshold of $p < 0.05$ family-wise error rate (FWE) corrected. Given the limited studies aimed at specifying brain differences in populations of childhood abuse, and to control for the false positive rate (using $p < 0.05$ FWE-corrected cluster statistics) while limiting potential Type II errors, an a-priori cluster-forming threshold of $p < 0.01$ for significant between-group differences was chosen.

ROI analyses were carried out using small volume correction in SPM8 for the following anatomical regions based on templates from the WFU_PickAtlas

(<http://fmri.wfubmc.edu/software/PickAtlas>). ROIs were selected based on brain regions reported as abnormal in individuals who had experienced childhood maltreatment (McCrory et al., 2011; Hart et al., 2012), including the amygdala, hippocampus, ACC, vmPFC, DLPFC and anterior cerebellum, corrected voxelwise for multiple comparisons at $p < 0.05$. MARSBAR (Brett et al., 2002) was used to extract beta values from the above ROIs for correlational analyses between neural activation and performance measures within each group and with abuse measures within the group of young people with a history of abuse only. For the neutral condition, correlations were also carried out between brain activation and percentage of negative and positive errors in the participants who had experienced abuse.

9.3. Results

9.3.1. Participant Characteristics

The groups did not differ significantly in age, gender, ethnicity or SES, but did differ in IQ, as expected (Table 9.1). Since lower IQ is associated with childhood maltreatment (De Bellis et al., 2009; Nolin and Ethier, 2007), artificially matching groups on IQ is considered inappropriate as it creates unrepresentative groups (Dennis et al., 2009). Also, covarying for IQ when groups are not randomly selected and the covariate is a pre-existing group difference that did not occur by chance violates ANCOVA assumptions (Dennis et al., 2009; Miller and Chapman, 2001). The primary data analyses are therefore presented without matching or covarying for IQ. However, to rule out any potential influence of IQ, additional confirmatory analyses of an ANCOVA covarying for IQ and correlational analysis of IQ with brain activation within each group were also conducted.

Although the study selected participants with severe childhood physical abuse, they also experienced marked/severe childhood emotional abuse and neglect (Table 9.1) which typically co-occur with physical abuse, and hence are a representative group of the population with childhood abuse (Edwards et al., 2003; Trickett et al., 2011).

Healthy controls scored significantly lower on BDI ($p < 0.01$) and all SDQ difficulties subscales ($p < 0.001$) than the participants who had experienced abuse, and on BDI ($p < 0.001$), SDQ emotional problems ($p < 0.001$) and hyperactivity ($p < 0.05$) subscales than psychiatric controls. Participants exposed to abuse scored significantly higher than psychiatric controls on SDQ conduct ($p < 0.01$) and peer problems ($p < 0.05$) subscales (Table 9.1).

9.3.2. Task Performance

Mean performance values are reported in Table 9.2. There were no significant group differences in percentage errors for any emotions ($F(10,120) = 0.8$; $p = 0.4$) but a trend for a group difference in reaction time ($F(10,120) = 1.6$; $p = 0.1$). Post-hoc analyses revealed that the participants who had experienced abuse responded faster than healthy controls for the fear condition ($p < 0.05$) and the psychiatric controls responded faster than healthy controls for neutral ($p < 0.01$), sad ($p < 0.05$) and anger ($p < 0.05$) conditions.

For neutral condition errors, the participants who had experienced abuse made significantly more negative errors than psychiatric controls ($t(38) = 1.07$, $p < 0.05$) and at a trend-level than healthy controls ($t(45) = 1.0$, $p = 0.09$).

TABLE 9.1. Demographic Characteristics of 20 Young People Exposed to Childhood Abuse, 20 Psychiatric Controls and 27 Healthy Controls

	Childhood Abuse (N=20)		Psychiatric Controls (N= 20)		Healthy Controls (N=27)		Analysis		Between Groups
	Mean	SD	Mean	SD	Mean	SD	F(2, 64)	p (corr.)	
Age (years)	17.5	2.44	16.8	2.62	17.5	1.63	0.90	0.40	-
[age range:13-20]									
Socioeconomic status	2.77	0.69	2.94	0.66	3.22	0.75	2.53	0.09	-
IQ	89.1	12.3	94.5	13.2	105.4	10.1	11.8	0.001	CA, PC < HC
SDQ:									
<i>Emotional problems</i>	4.85	2.62	4.85	2.91	1.92	1.61	11.6	<0.001	CA, PC > HC
<i>Conduct problems</i>	4.30	2.23	2.40	2.30	1.68	1.60	9.55	<0.001	CA > PC, HC
<i>Hyperactivity</i>	5.75	2.0	4.85	2.68	2.84	2.14	9.75	<0.001	CA, PC > HC
<i>Peer problems</i>	3.70	1.66	2.40	1.98	1.16	1.72	11.2	<0.001	CA > PC, HC
<i>Prosocial</i>	7.25	1.62	8.40	1.90	8.08	1.41	2.65	0.08	-
<i>Total difficulties score</i>	18.6	6.67	14.5	6.20	7.60	5.73	16.3	<0.001	CA, PC > HC
Beck's Depression Inventory	17.0	10.0	20.9	11.8	5.92	6.09	9.04	< 0.001	CA, PC > HC
CTQ:									
<i>Physical abuse</i>	21.1	5.0	6.11	1.60	5.52	0.94	98.8	<0.001	CA > PC, HC
<i>Emotional abuse</i>	17.7	4.50	7.05	1.84	6.04	1.13	84.3	<0.001	CA > PC, HC
<i>Sexual abuse</i>	5.15	0.67	5.53	1.03	5.11	0.42	1.83	0.20	-
<i>Physical neglect</i>	13.3	5.31	6.84	2.22	5.59	1.22	26.8	<0.001	CA > PC, HC

<i>Emotional neglect</i>	17.6	4.50	8.90	3.76	7.93	3.35	35.7	<0.001	CA > PC, HC
Age at onset of (physical) abuse (years)	3.85	2.74							
Duration of (physical) abuse (years)	8.55	3.07							
	N	%	N	%	N	%	χ^2	<i>p</i>	Between Groups
Gender (Males)	14	70	10	50	19	70.4	2.49	0.29	-
Ethnicity:							9.09	0.06	-
<i>Caucasian</i>	10	50	3	15	13	48			
<i>Afro-Caribbean</i>	8	40	11	55	12	44			
<i>Others (Asian/mixed)</i>	2	10	6	30	2	8			
Psychiatric diagnosis:									
<i>PTSD</i>	12	60	12	60	-				
<i>Depression</i>	6	30	6	30	-				
<i>Anxiety disorders</i>	5	25	5	25	-				
<i>Social phobia</i>	1	5	1	6	-				
<i>ADHD</i>	1	5	1	5					
<i>ODD/CD/Other disruptive behaviors</i>	5	25	4	20	-				

Abbreviations: CA=Childhood Abuse; PC=Psychiatric Controls; HC=Healthy Controls; corr=Bonferroni corrected; CTQ=Childhood Trauma Questionnaire; SDQ=Strength and Difficulties Questionnaire; ADHD=Attention Deficit Hyperactivity Disorder; PTSD=Post-Traumatic Stress Disorder; ODD=Oppositional Defiant Disorder; CD=Conduct Disorder

TABLE 9.2. Performance Measures for the Emotion Processing Task for 20 Young People Exposed to Childhood abuse, 20 Psychiatric Controls and 27 Healthy Controls

	Childhood Abuse (N=20)		Psychiatric Controls (N= 20)		Healthy Controls (N=27)	
	Mean	SD	Mean	SD	Mean	SD
Neutral MRT	611	106	570	84.2	662	123
Fearful MRT	657	133	685	152	739	122
Angry MRT	656	108	632	112	719	119
Sad MRT	653	111	624	84.5	716	130
Happy MRT	586	89.9	578	103	624	104
Neutral Mean Number Neg Errors	6	5.0	2.5	1.5	3.2	2.1
Neutral Mean Number Pos Errors	4.9	2.7	2.5	1.6	3.0	2.3

Abbreviations: MRT=Mean Reaction Time (in ms); Neg=Negative; Pos=Positive

9.3.3. Brain Activation

Motion

MANOVAs showed no significant group differences in maximum translation ($F(6,124) = 1.0, p > 0.05$) or maximum rotation ($F(6,124) = 1.52, p > 0.05$) parameters.

Whole-Brain Analyses

Within group activations are shown in Figure 9.2. For between-group activation, ANOVAs revealed no effect of group for angry, sad or happy conditions vs fixation; but revealed significant group effects in a cluster of bilateral vmPFC and ACC for fear vs fixation and in a cluster encompassing the amygdala, anterior cerebellum, parahippocampal gyrus, IFC, inferior, middle and superior temporal gyri for neutral vs fixation.

For fear vs fixation, post-hoc analyses showed that individuals exposed to abuse relative to healthy controls had increased activation in a large bilateral cluster in vmPFC and ACC reaching subcortically into the caudate (Table 9.3, Figure 9.3A). To explore differences between the childhood abuse and psychiatric control groups, a more lenient threshold of $p < 0.05$ uncorrected was used showing that the participants who had experienced abuse also demonstrated increased activation of bilateral vmPFC and ACC compared to psychiatric controls (Figure 9.4A).

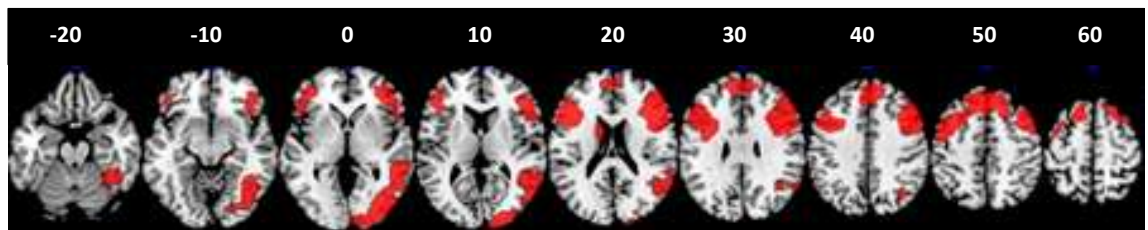
For neutral vs fixation, post-hoc analyses showed that the participants with a history of abuse, relative to psychiatric controls, had increased activation in a large bilateral cluster peaking in the amygdala and extending bilaterally into the parahippocampal gyrus, inferior, middle and superior temporal gyri, anterior cerebellum, brainstem, putamen, globus pallidus and IFC, and in the left hemisphere into hippocampus, thalamus and caudate (Table 9.3, Figure 9.3A). At $p < 0.05$ uncorrected, the participants who had experienced abuse also demonstrated increased activation of the amygdala, hippocampus and anterior cerebellum compared to healthy controls (Figure 9.4B).

When directly contrasting fear with neutral, there were no group differences observed at $p < 0.05$ corrected at cluster level. However, with an uncorrected $p < 0.05$ threshold, the participants who had experienced abuse had increased activation relative to healthy controls bilaterally in vmPFC and ACC, left caudate and right precuneus (Figure 9.4C) and relative to psychiatric controls in bilateral ACC and left vmPFC and caudate (Figure 9.4D). To explore the effect of IQ, data were re-analysed with IQ as a covariate. All findings remained significant (Figure 9.5).

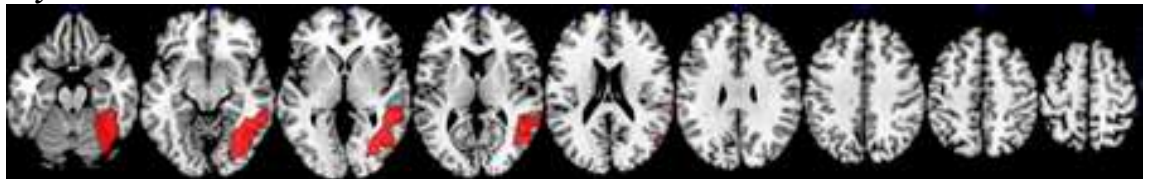
FIGURE 9.2. Within-Group Brain Activation for each Emotion Condition vs Fixation

Fear

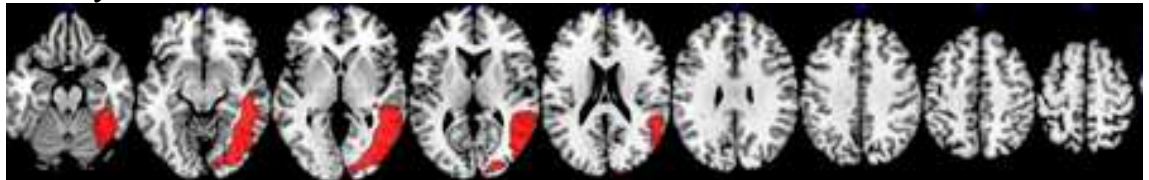
Childhood Abuse



Psychiatric Controls

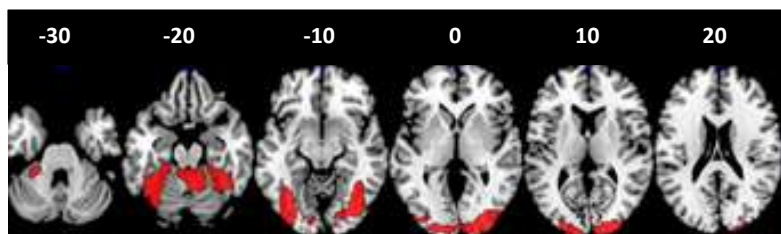


Healthy Controls



Neutral

Childhood Abuse

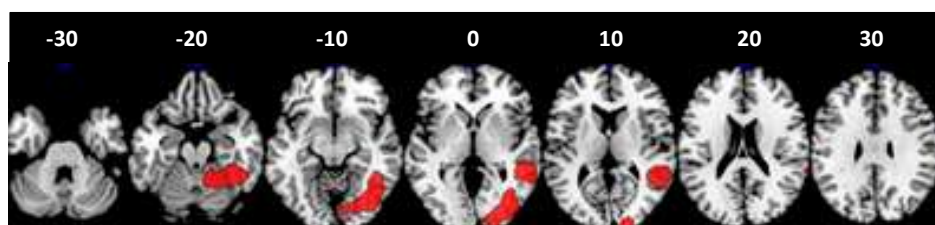


Psychiatric Controls: None

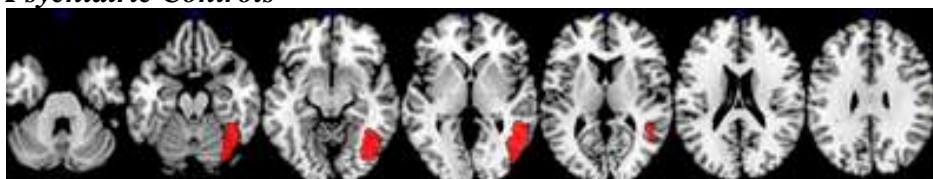
Healthy Controls: None

Anger

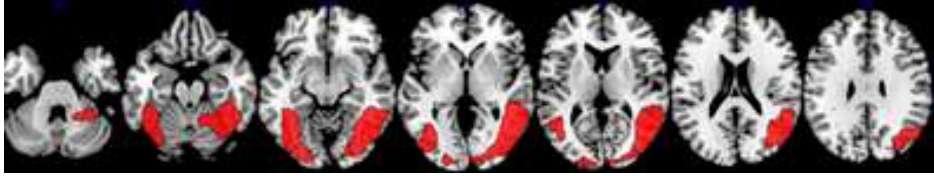
Childhood Abuse



Psychiatric Controls

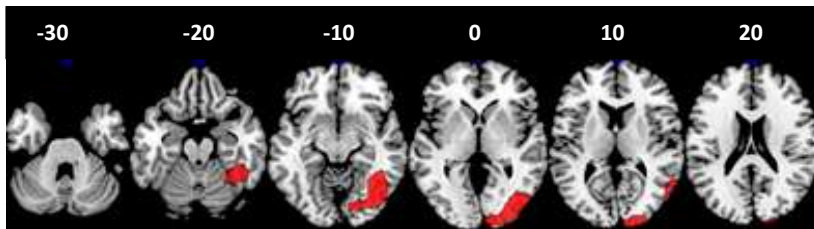


Healthy Controls

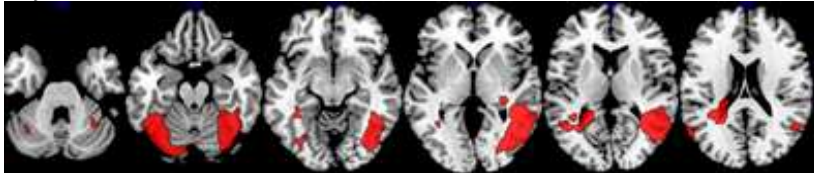


Sad

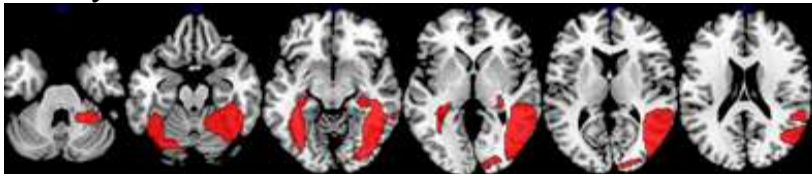
Childhood Abuse



Psychiatric Controls



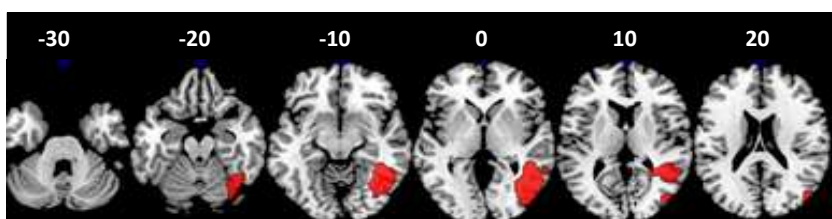
Healthy Controls



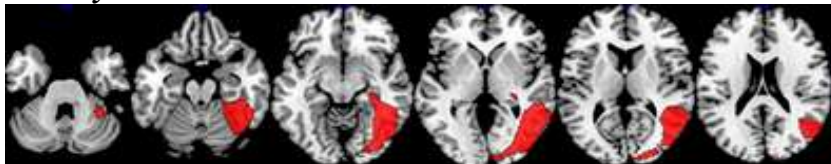
Happy

Childhood Abuse: None

Psychiatric Controls



Healthy Controls



Axial sections showing within-group brain activation during each emotion condition vs fixation in 20 young people exposed to childhood abuse, 20 psychiatric controls and 27 healthy controls, $p < 0.05$, FWE-corrected at the cluster level. Axial slices are marked with the z coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain

TABLE 9.3. Regions of Differential Brain Activation for Fear and Neutral vs Fixation between 20 Young People Exposed to Childhood Abuse, 20 Psychiatric Controls and 27 Healthy Controls

Emotion	Brain Region	BA	Cluster Level		Peak MNI Coordinates	Analysis
			No. of Voxels	<i>p</i> (corr.)		
Fear	<u>Childhood Abuse > Healthy Controls</u>					
	Bilateral medial/superior frontal/precentral gyri / anterior cingulate cortices/caudate body	9/10/8/6/24/32	4625	0.002	-6,50,8	WBA
	Left orbitofrontal cortex		5	0.038	-6,50,8	ROI
	Bilateral Anterior cingulate cortices		38	0.023	-4,48,8	ROI
			3	0.043	4,48,6	
Neutral	<u>Childhood Abuse > Psychiatric Controls</u>					
	Bilateral amygdala, anterior cerebellum/ brainstem/red nucleus/substantia nigra/inferior/middle/superior temporal gyri/uncus/parahippocampal/putamen/globus pallidus/IFC/Left thalamus/caudate tail/ hippocampus	20/21/37/38/28/34/35/36/47	7590	0.001	-28,-2,-22	WBA
	Bilateral amygdala		75	0.028	-28,-2,-22	ROI
			14	0.048	24,0,-24	
			8	0.044	22,-10,-10	
			6	0.045	20,-4,-14	
	Left hippocampus		14	0.041	-30,-10,-22	ROI
	Bilateral anterior cerebellum		352	0.003	-6,-48,-26	ROI
		3	0.045	-22,-32,-20		

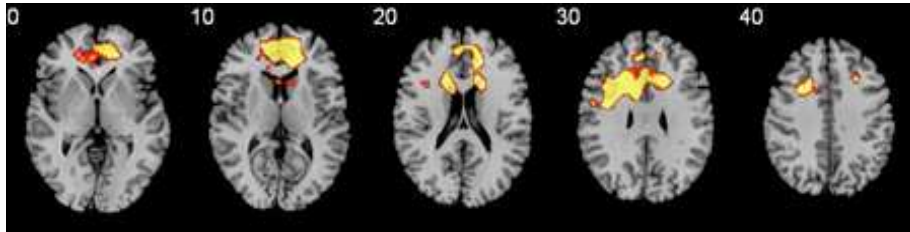
Abbreviations: MNI= Montreal Neurological Institute; corr=FWE-corrected; BA=Brodmann's Area; WBA=Whole-Brain Analysis; ROI=Region-of-Interest; IFC=Inferior frontal cortex

FIGURE 9.3. Brain Activation for Fear and Neutral Conditions vs Fixation in Young People Exposed to Childhood Abuse compared to Healthy and Psychiatric Controls, at $p < 0.05$ corrected

A) Whole-brain Analysis

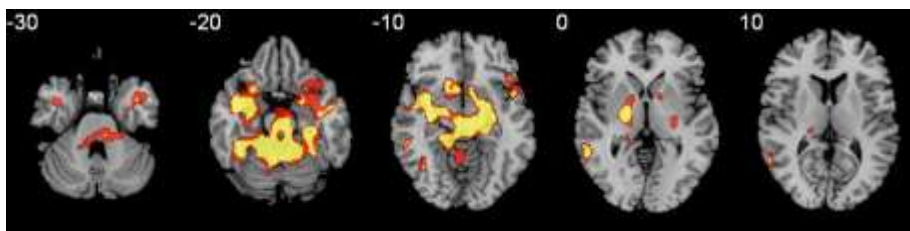
Fear vs Fixation

Childhood Abuse > Healthy Controls



Neutral vs Fixation

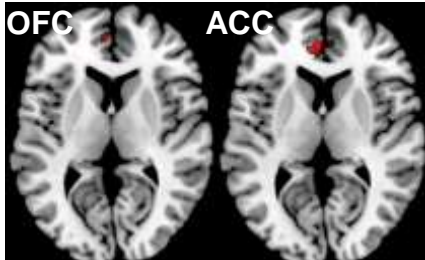
Childhood Abuse > Psychiatric Controls



B) Region-of-Interest Analysis

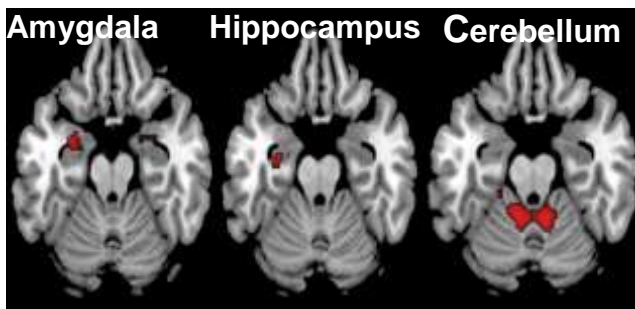
Fear vs Fixation

Childhood Abuse > Healthy Controls



Neutral vs Fixation

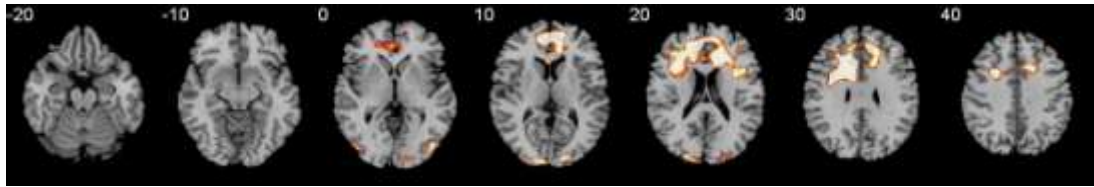
Childhood Abuse > Psychiatric Controls



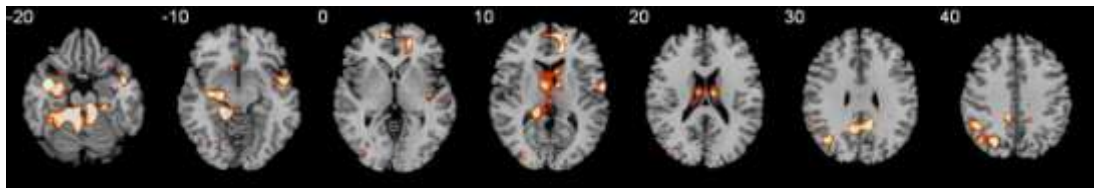
Axial sections showing increased brain activation for fear and neutral vs fixation in 20 young people exposed to childhood abuse, 20 psychiatric controls and 27 healthy controls using A) whole-brain analysis, $p < 0.05$ FWE-corrected at cluster level; and B) Region-of-Interest analysis, $p < 0.05$ -corrected. Axial slices are marked with the z coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

FIGURE 9.4. Brain Activation for Fear and Neutral Conditions in Young People Exposed to Childhood Abuse compared to Healthy and Psychiatric Controls, at $p < 0.05$ uncorrected

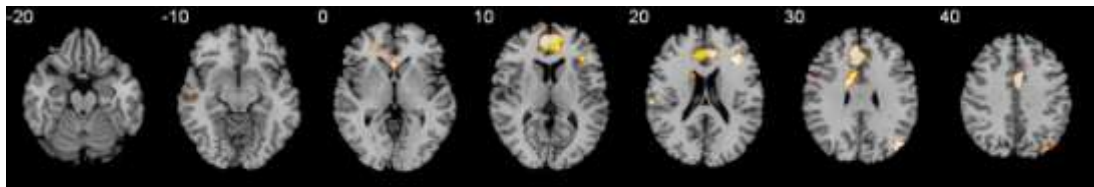
A) Fear vs Fixation *Childhood Abuse > Psychiatric Controls*



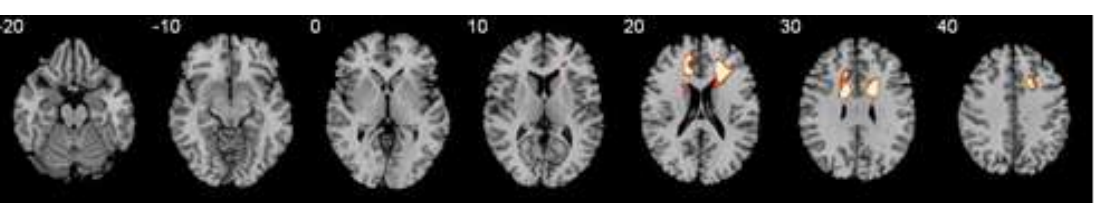
B) Neutral vs Fixation *Childhood Abuse > Healthy Controls*



C) Fear vs Neutral *Childhood Abuse > Healthy Controls*

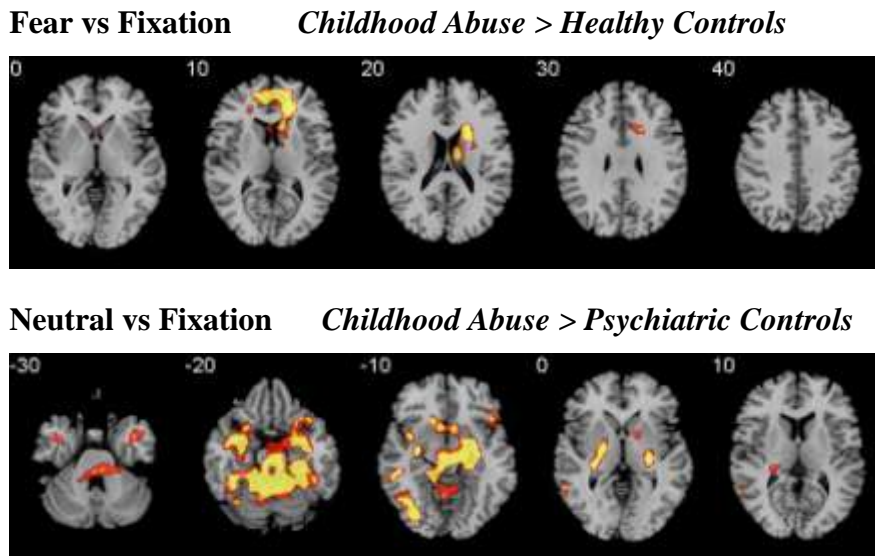


D) Fear vs Neutral *Childhood Abuse > Psychiatric Controls*



Axial sections showing brain activation in 20 young people exposed to childhood abuse, 20 psychiatric controls and 27 healthy controls for A) fear vs fixation, B) neutral vs fixation and C), D) fear vs neutral, $p < 0.05$ uncorrected. Axial slices are marked with the z coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

FIGURE 9.5. Brain Activation for Fear and Neutral Conditions vs Fixation in Young People Exposed to Childhood Abuse compared to Healthy and Psychiatric Controls with IQ as a Covariate



Axial sections showing brain activation for fear and neutral vs fixation in 20 young people exposed to childhood abuse, 20 psychiatric controls and 27 healthy controls with IQ as a covariate, $p < 0.05$ FWE-corrected at cluster level. Axial slices are marked with the z coordinate as distance in millimetres from the anterior–posterior commissure. The right side of the image corresponds to the right side of the brain.

ROI analyses

ROI analyses for fear vs fixation revealed greater activation for the participants who had experienced abuse, compared to healthy controls, bilaterally in ACC and in left vmPFC (Table 9.3, Figure 9.3B). For neutral vs fixation, the participants with a history of abuse had greater activation compared to psychiatric controls in bilateral amygdala and anterior cerebellum and in left hippocampus (Table 9.3, Figure 9.3B). No findings were significant for fear vs neutral.

Correlational Analyses

In the group of participants who had experienced abuse, amygdala activation for neutral vs fixation was positively correlated with the percentage of negative errors, so that increased amygdala activation was related to increased perception of neutral faces as negative ($r = 0.27$, $p = 0.028$). No significant correlations were found between brain activation and IQ, reaction time or abuse measures within each group.

9.4. Discussion

Young people with a history of severe childhood abuse exhibited altered processing of neutral and fearful facial expressions relative to healthy and psychiatric controls. Behaviourally, the participants who had experienced abuse responded faster to fearful faces than healthy controls and were more inclined to perceive neutral faces as having a negative valence relative to both control groups. In addition, they exhibited increased activation in fronto-limbic networks relative to healthy and psychiatric controls during fear and neutral face processing. Furthermore, enhanced amygdala activation for neutral faces positively correlated with the percentage of neutral expressions perceived to be negative.

The findings suggest that young people with a history of abuse are hypersensitive to fear relative to healthy controls both at performance (faster response) and brain level (fronto-limbic hyperactivation). They also demonstrated, at a more lenient threshold, hyperactivation of fronto-limbic regions relative to psychiatric controls, suggesting that this effect may be abuse-specific. Hypersensitivity to fear is consistent with previously reported response biases for negative emotions and altered brain activity to fearful faces in childhood

maltreatment (Taylor et al., 2006; Masten et al., 2008; Maheu et al., 2010; Tottenham et al., 2011; Dannlowski et al., 2012a; Garrett et al., 2012; Caldwell et al., 2014; Crozier et al., 2014). It is plausible that the young people who had experienced severe childhood physical abuse respond faster to fearful faces because they have experienced fear more frequently than non-maltreated individuals and are therefore more sensitive to and able to recognise fear quickly.

Contrary to expectation, the participants who had experienced abuse did not show an enhanced activation to angry faces compared to previous studies (Maheu et al., 2008; McCrory et al., 2011, 2013; Garrett et al., 2012). However, this must be considered with reference to the methodological differences between the present and earlier studies. For instance, it is worth noting that participants in the present study had experienced more severe level of childhood maltreatment (CTQ scores were classified as severe/extreme: scored > 13 for physical abuse, > 16 for emotional abuse, > 17 for emotional neglect and >13 for physical neglect) compared to the participants in previous studies (McCrory et al., 2011, 2013; mean abuse subtype severity scores ranged from 1.5 to 2.8 on Kaufman's four-point scale), while Garrett et al (2012) recruited patients with childhood maltreatment-related PTSD and Maheu et al (2008) studied youths who had experienced caregiver deprivation only; hence, the findings may not be directly comparable. It is also possible that the anger stimuli used in the present study was of lower intensity than what these individuals with a history of severe/*extreme* childhood abuse had been typically exposed to in their home environments compared to the earlier studies. Additionally, the participants in the current study were older (mean age =17.5 years) and had experienced childhood abuse before the age of 12 years old; while Pollack and colleagues (Pollack et al., 1997, 2000, 2001, 2005; Pollak and Kistler, 2002; Pollak and Sinha, 2002) examined

emotion processing in children with a maximum mean age of 9 years old and the participants in the studies of McCrory et al (2011, 2013) were 12 years old on average. Hence, it is possible that angry expressions could still serve as highly salient and threatening emotional cues in the earlier studies due to the more recent nature of their maltreatment experiences. Although both fearful and angry facial expressions may indicate the presence of a threat, fearful faces are more ambiguous than angry faces which provide information about the specific source of a threat (Whalen, 1998). The young people in the present study were not at any current risk of parental maltreatment; hence, the increased sensitivity to fearful and not angry faces may possibly stem from their more extensive personal experience of fear. Finally, the current finding of hypersensitivity to fearful but not angry faces is also consistent with the findings that childhood maltreatment in adolescents was *uniquely* and positively associated with recognition of fearful but not angry faces, where higher levels of maltreatment corresponded with better recognition of fear (Leist and Dadds, 2009).

When observing fearful faces, the participants with a history of abuse demonstrated increased activation of vmPFC and ACC relative to healthy controls, and at a more lenient threshold relative to psychiatric controls. This is consistent with the concept that the vmPFC and ACC play a role in fear processing and in appraisal of negative emotions and regulating the generation of emotional responses via the limbic system (Phelps et al., 2004; Milad et al., 2007; Hansel et al., 2008; Etkin et al., 2011). Thus the observed hyperactivation of the vmPFC and ACC to fear in the participants who had experienced abuse may occur as they exert extra effort to suppress negative emotional responses elicited by their heightened sensitivity to fear.

The perception of neutral facial expressions as negative by the participants exposed to abuse may stem from a hypervigilance to negative threatening expressions and is consistent with the finding that neutral faces were most commonly perceived as angry and sad by highly maltreated children (Leist and Dadds, 2009). When viewing neutral faces, the participants who had experienced abuse demonstrated increased activation of the amygdala, hippocampus and cerebellum relative to psychiatric controls, and at a more lenient threshold, relative to healthy controls. In addition, they also demonstrated hyperactivation relative to psychiatric controls in the parahippocampal gyrus, temporal lobe, brainstem, basal ganglia, IFG and thalamus. Amygdala activation correlated with the percentage of neutral faces perceived as negative suggesting that the amygdala may be more active in the participants exposed abuse, who were more likely to view neutral expressions as negative. The altered amygdala activation to neutral faces contrasts with results of a study of previously institutionalised children reporting no change (Tottenham et al., 2011), possibly due to differences in maltreatment type. The limbic system, in particular the amygdala, plays a key role in emotion processing, assessment of threatening information, fear conditioning and emotional memory (Davis and Whalen, 2001). There is also increasing recognition that the IFC, cerebellum and basal ganglia are involved in emotion processing (Nakamura et al., 1999; Adolphs, 2002; Schmahmann and Caplan, 2006). As the young people with a history of abuse perceived neutral faces more emotionally (negatively) than controls, it appears that this is concomitant with abnormally enhanced activation of (negative) emotion-mediating brain regions when viewing neutral faces.

The strength of this study is that all participants were medication-naïve, drug-free and that the abuse experience was carefully assessed and corroborated by social service records. Also, a psychiatric control group was included to determine the specificity of abuse. It is important to use dynamic stimuli as they are more ecologically valid than static faces, and facial movements have been shown to contribute to the identification of facial expressions (Simon et al., 2008). However, it is unclear to what extent pubertal development, malnutrition and prenatal drug exposure may have influenced the findings. The SES measure is limited without information on parents' income and education; however, youth often have difficulties in reporting this information (Currie et al., 1997). Although childhood sexual abuse was excluded as it has been shown to differ in many aspects (Ackerman et al., 1998) including distinctive effects on the somatosensory cortex (Heim et al., 2013), it is unrealistic to separate physical abuse from typically co-occurring emotional abuse and neglect (Edwards et al., 2003; Trickett et al., 2011). Finally, the interpretation of the findings may be limited by the use of a non-facial stimulus (i.e. fixation condition) as the baseline condition since brain activation related to emotion processing may have been confounded by face perception. However, the present study also underscores the caveat of using a neutral face condition as contrast condition in studies investigating neural correlates of emotion processing in childhood maltreatment since the participants who had experienced abuse tended to perceive "neutral" faces as negative rather than as neutral stimuli. Future studies may consider using additional baseline conditions such as scrambled faces or neutral faces morphed to a mild (e.g., 25%) "happy" intensity in order to avoid appearing negative (Phillips et al., 1998) particularly for participants who had experienced childhood abuse.

In summary, severe childhood abuse is associated with abnormally elevated fronto-limbic fear and neutral face processing, suggesting that childhood abuse may possibly lead to sensitisation to fearful faces and a negative perception bias to neutral face processing. Hypersensitivity to fear and misinterpreting neutral emotional stimuli as negative could have adverse consequences for social interaction and this knowledge may help to develop new interventions to address social information errors using neuro-feedback or extinction approaches.

CHAPTER 10

General Discussion and Conclusions

10.1. Objectives and Novelty of the Study

There is an increasing interest in understanding the effects of early environmental adversities such as childhood maltreatment on the developing brain. The experience of maltreatment during childhood not only causes the individual pain and distress at the time but also acts as a severe stressor that produces a cascade of physiological and neurobiological changes that lead to enduring alterations in brain structure and function. Moreover, childhood maltreatment is significantly associated with first onsets of various psychiatric disorders including mood, anxiety and PTSD (Green et al., 2010) and with several neuropsychological deficits such as impaired attention, inhibitory control and emotion processing (Chapter 2). It has been further suggested that the psychopathological outcomes associated with childhood maltreatment may be mediated by the disruption of cognitive processes and their associated neural underpinnings (Bremner and Vermetten, 2001).

Therefore, to advance our understanding of the deleterious effects of childhood maltreatment on the developing brain, I conducted a meta-analysis of published whole-brain VBM studies in childhood maltreatment to elucidate the most robust volumetric GM abnormalities relative to non-maltreated controls (Chapter 6), and examined the association between severe childhood (physical) abuse and neurofunctional abnormalities in three functional domains using fMRI in medication-naïve, drug-free young people, controlling for psychiatric comorbidities by including a third group of psychiatric controls. The fMRI study focused on response inhibition

and error processing (Chapter 7), sustained attention (Chapter 8) and emotion processing (Chapter 9). The inclusion of a psychiatric control group is crucial as currently most studies did not control for psychiatric comorbidities making it unclear whether the neurobiological abnormalities observed can be attributed to childhood maltreatment, or the associated psychiatric conditions, or a combination of both. It is also imperative to control for drug abuse as it has been shown to affect brain structure and function (Goldstein and Volkow, 2011) as well as to control for psychoactive medications as they are also known to affect brain structure and function (Murphy, 2010; Nakao et al., 2011), so that the reported brain abnormalities associated with childhood maltreatment are not confounded by long-term medication and/or drug effects.

The novelty of this PhD project includes being the first study to conduct a meta-analysis of published whole-brain VBM studies of structural abnormalities in childhood maltreatment. It is also the first fMRI study to examine the neurofunctional correlates of error processing and sustained attention in (severe) childhood abuse. Furthermore, this project is only the second fMRI study to-date that has included a psychiatric control group to examine the neural correlates of emotion processing in childhood abuse, in a relatively larger sample than the previous study (Grant et al., 2011). This previous study is also limited by the use of self-report measure to evaluate childhood trauma given the known relationship between current mood and memory (Grant et al., 2011), and it only examined the neural processing of sad faces within MDD which may limit the generalizability of the findings to individuals who had experienced childhood abuse and have other psychiatric disorders besides MDD.

10.2. Discussion of Findings

The present meta-analysis findings of 12 whole-brain structural MRI studies in 331 individuals exposed to childhood maltreatment and 362 non-maltreated controls showed that the most consistent GM abnormalities in childhood maltreatment were in relatively late-developing right OFC and superior temporal gyrus, reaching into limbic areas such as amygdala, insula and parahippocampal gyrus as well as left IFC; regions that are known to mediate late-developing affective (OFC, limbic and temporal areas) as well as cognitive (left IFC) control. Furthermore, the findings were independent of medication effects as they remained in the subgroup analysis of unmedicated participants (Chapter 6). Thus, childhood maltreatment is associated with abnormalities in the orbitofrontal-temporo-limbic regions that form the paralimbic system, which is known to be implicated in emotion and motivational processing and the self-regulation of social-emotional behaviours (Bonelli et al., 2007; Dolan et al., 2007; Zahn et al., 2007), and may possibly be related to the typical development of common psychiatric comorbidities, particularly depression and PTSD, which have also been associated with GM abnormalities in these orbitofrontal and limbic regions (Rauch et al., 2006; Koolschijn et al., 2009). Individuals with a history of childhood maltreatment also exhibited deficits in the left IFC which is part of the ventral attention system (Cole and Schneider, 2007), mediating saliency detection, action selection and sustained attention (Swick et al., 2008; Cubillo et al., 2012; Rubia et al., 2009a,b).

The fMRI findings of this PhD project are in line with the meta-analysis findings in that both affect-mediating paralimbic brain regions as well as cognitive

brain regions were found to be functionally impaired in the context of the three different fMRI tasks.

During failed inhibition, the participants who had experienced childhood abuse showed abnormally enhanced activation in typical error processing regions of the dorsomedial frontal cortex including bilateral pre-SMA/SMA, dorsal ACC and superior frontal gyri relative to healthy controls and in a smaller cluster of the SMA relative to psychiatric controls. They were also slower in their response after errors compared to healthy controls (Chapter 7). No group differences in activation were observed for successful inhibition (Chapter 7).

During sustained attention, the participants exposed to childhood abuse exhibited reduced activation in typical dorsal and ventral sustained attention regions of left DLPFC and IFC, ACC/pre-SMA/SMA, bilateral striato-thalamic, cingulate and cerebellar areas relative to healthy controls during the most challenging attention condition only. The left IFC underactivation in particular is interesting as it overlapped with the meta-analytical structural imaging findings of reduced GM in left IFC. Furthermore, although the activation deficits were not abuse-specific as they did not survive comparison to psychiatric controls, there was an abuse-specific linear trend of decreasing activation with increasing attention loads in these regions relative to psychiatric controls (Chapter 8). This suggests that young people with a history of childhood abuse, but not the healthy or psychiatric control groups, deteriorated in the activation of their attention networks with increasing attention load leading to impairment during the most difficult condition only. This was also reflected in their

greater number of omission errors, albeit at a trend-level, in the most demanding condition compared to healthy controls.

During fear processing, the participants with a history of abuse demonstrated abnormally heightened activation of classical fear processing regions of bilateral vmPFC and ACC relative to healthy and psychiatric controls along with increased activation in the caudate relative to healthy controls. Their heightened sensitivity to fear is also reflected in their faster response to fearful faces than healthy controls. During neutral face processing, the participants who had experienced abuse had increased activation in a large bilateral cluster peaking in the amygdala and extending bilaterally into the parahippocampal gyrus, inferior, middle and superior temporal gyri, anterior cerebellum, putamen, globus pallidus and IFC, and in the left hemisphere into hippocampus, thalamus and caudate tail relative to psychiatric controls. They also had increased activation in some of these regions including the amygdala, hippocampus and anterior cerebellum relative to healthy controls. The increased activation of the vmPFC and ACC to fearful faces is consistent with their role in the appraisal of negative emotions and regulating or suppressing the generation of emotional responses via the limbic system (Phelps et al., 2004; Milad et al., 2007; Hansel et al., 2008; Etkin et al., 2011); hence, the hyperactivation of the vmPFC and ACC may occur as these individuals who had experienced abuse exert extra effort to suppress the negative emotional responses elicited by their heightened sensitivity to fear. Finally, the young people exposed to childhood abuse were more inclined to perceive neutral faces as having a negative valence than their non-maltreated counterparts, which were furthermore correlated with enhanced activation of the amygdala in processing neutral faces (Chapter 9).

10.2.1. Abnormally Enhanced Activation during Error Monitoring and Fear Processing

The findings of abnormally enhanced activation of error monitoring regions and fear processing regions in the group with a history of childhood abuse are interesting and may be closely interrelated. The hypersensitive error monitoring system could possibly be the cognitive counterpart of evidence from the emotion processing task of enhanced fear processing. For instance, it is plausible that the young people with a history of severe childhood (physical) abuse may exhibit abnormally enhanced error-related brain activation due to the constant need to monitor their actions in order to avoid potential painful mistakes that are often associated with danger in an abusive context and hence with fear, which indicates the presence of danger in the immediate environment (Whalen et al., 1998, 2001). The participants with a history of abuse did not show an enhanced activation to angry faces, possibly because the anger stimuli used in the experiment was of lower intensity than what these individuals who had experienced *severe* childhood abuse had been typically exposed to in their home environments. The participants with a history of abuse showed abnormally increased brain activation in the SMA relative to both healthy and psychiatric controls, suggesting that the hyperactivation of this key error processing region may be abuse-specific. They also evinced abnormally enhanced abuse-specific activation of vmPFC and ACC during fear processing. Hence, it is possible that the persistent harsh punishment experiences in childhood may have sensitized the child to fear and to errors, signalling potential danger and punishment, and led to an overactive fear and error monitoring system as evidenced by the findings of faster response and increased activation to fearful faces as well as a slower post-error reaction time and a hypersensitive error-related SMA activation. These findings would be in line with evidence that environmental adversities such as

punishment and punitive parenting lead to lasting enhanced error-related negativity in ERP studies of children and young people (Riesel et al., 2012; Meyer et al., 2014) and are associated with childhood anxiety and dysfunctional fear processing in children (Hadwin et al., 2006; Field et al., 2007).

The heightened neural response to negative affect and to errors may possibly be functionally beneficial to survive in an abusive environment by improving the ability to identify threatening situations rapidly and correct mistakes so as to shield against potential violence. Nonetheless, it may incur long-term costs for the affected individual by limiting attentional resources for mastering age-appropriate cognitive and social skills and may also increase the vulnerability to develop psychopathology in the future (Shackman et al., 2007; McCrory et al., 2011, 2013).

10.2.2. Reduced Activation in Sustained Attention Regions

In the cognitive domain, the participants with a history of abuse had no deficits in response inhibition, but showed sustained attention deficits in the most difficult attention condition only. This PhD project is the first to examine and report an association between severe childhood (physical) abuse and brain functional abnormalities during sustained attention (Chapter 8). The findings of reduced activation in typical dorsal and ventral fronto-striato-thalamo-cerebellar sustained attention regions during the most challenging attention condition only suggest that neurofunctional abnormalities during sustained attention in the individuals who had experienced abuse are intact in easier attention conditions and manifest only during the most challenging condition. This is interesting in view of neurofunctional deficits in the identical task in patients with ADHD and ASD (Christakou et al., 2013;

Murphy et al., 2014) in all attention conditions. Thus, young people exposed to childhood abuse appear to show less neurocognitive impairment during sustained attention than psychiatric disorders associated with attention deficits (e.g. ADHD, ASD), as the deficits only manifest at the more challenging attention conditions.

The linear trend of decreasing activation with increasing attention loads in these regions in the participants with a history of abuse but not in the healthy or psychiatric controls suggest that the deterioration of attention functions with longer periods of continuous focus was abuse-specific relative to psychiatric controls. Furthermore, the findings of a deficit in both top-down frontal executive attention control and bottom-up visual-spatial saliency processing in the individuals exposed to abuse especially in the left IFC, left precentral and right parahippocampal gyri may be related to the meta-analytic findings of structural abnormalities in these regions.

10.2.3. Spared Inhibitory Function

However, the hypothesis that childhood abuse is associated with inhibitory dysfunction was not supported. The lack of significant group differences in brain activation during response inhibition is consistent with the negative findings of a previous fMRI study that used the same stop-signal paradigm which instead reported significant effects of childhood maltreatment on the functional connectivity of the inhibitory control network (Elton et al., 2013). The participants who had experienced abuse also demonstrated normal inhibitory capacity which is consistent with previous performance findings (Carrion et al., 2008; Elton et al., 2013). Although the other two studies found impaired inhibitory activation, they used the go/no-go (Carrion et

al., 2008) and stop-change (Mueller et al., 2010) tasks and recruited youths who experienced early deprivation (Mueller et al., 2010) and adolescents with PTSS and childhood trauma such as sexual abuse and witnessing violence (Carrion et al., 2008), which were not included in this project. Hence, the findings are not directly comparable. Although childhood maltreatment is not associated with functional deficits of individual brain regions during response inhibition, it might alter the functional connectivity comprising the inhibitory control networks; hence, future studies are needed to examine the integrity of inhibitory networks in youth exposed to different types of maltreatment.

10.2.4. Summary

Therefore, this PhD project shows that young people who had experienced childhood abuse did not exhibit global impairments in either the cognitive or the emotion domain. Instead, in the cognitive domain, they had performance and brain function abnormalities in error processing networks, but had intact performance and brain function during inhibitory control. The deficits in sustained attention networks only manifested during the most challenging attention condition where they also made more omission errors, albeit at a trend-level, than healthy controls. In the emotional domain, they showed normal brain activation and performance to all emotions except for fearful and neutral emotions. Thus, the young people who had experienced abuse showed a heightened sensitivity to signs or cues (e.g. errors, fearful faces) that may signal potential danger and threat. The development of an increased sensitivity to errors and fearful facial expressions may be particularly adaptive if it is associated with imminent danger; however, this prolonged hyper-reactivity in the absence of any real threat may increase the vulnerability to

psychopathology in the future. Furthermore, the abnormally elevated activation in fronto-striato-temporo-limbic and cerebellar regions to neutral faces and the negative perception bias of neutral faces is similar to that observed in depression and anxiety disorders (Cooney et al., 2006; Maniglio et al., 2014) and is thus likely to be maladaptive.

10.2.5. Specificity of Abnormalities Relative to Psychiatric Controls

An important question addressed by this PhD project is: what is the effect of childhood maltreatment on the developing brain independently of these comorbidities and to what extent does the combination of childhood maltreatment and psychiatric disorders differ in its neurobiology from that of psychiatric disorders alone. Thus, in order to assess the specificity of the association with childhood abuse, this project included a third group of psychiatric controls and indeed observed some interesting deficits specific to the abuse relative to the psychiatric controls. The novelty findings of this project include an abuse-specific abnormally enhanced activation in key error processing region of the SMA (Chapter 7) and an abuse-specific abnormally enhanced activation in vmPFC and ACC regions of fear processing apparently reflecting hypervigilance to potential danger (Chapter 9). The young people who had experienced abuse also had an abuse-specific abnormally heightened activation in the amygdala, hippocampus and anterior cerebellar regions when processing neutral faces where the hyperactivation in the amygdala was furthermore positively associated with the percentage of neutral faces perceived to be negative. Given that the participants exposed to abuse showed functional impairment in the dorsal and ventral fronto-striato-thalamo-cerebellar sustained attention regions relative to healthy controls only, the deficits may possibly be abuse-related and are

associated with the combination of the abuse experience and psychiatric comorbidities since the psychiatric controls did not differ significantly from the healthy controls or the participants with a history of abuse. Conceivably, childhood abuse and impaired sustained attention may possibly be linked through a pathway related to the development of psychiatric comorbidities. Moreover, although the activation deficits *per se* were not different between the participants who had experienced abuse and the psychiatric controls, the linear trend findings of a progressively deteriorating activation across all attention conditions/delays was abuse-specific relative to the psychiatric controls. That is, the participants with a history of abuse appear to exhibit progressively weaker brain activation with increasing delays and this progressive deterioration is abuse-specific relative to the psychiatric controls (Chapter 8). Importantly, all the findings remained significant controlling for IQ; hence, IQ differences were unlikely to explain the findings.

10.2.6. Parallel Findings between the Structural Meta-Analysis and Functional fMRI Data

Interestingly, the association between childhood abuse and functional abnormalities in some regions such as the left IFC during sustained attention, the left precentral gyrus during sustained attention and error processing, the right parahippocampal gyrus during sustained attention and processing of neutral faces as well as the right OFC, middle and superior temporal gyri and amygdala during processing of neutral faces in the fMRI study is further parallel to the meta-analytical findings of structural abnormalities in these relatively late-developing cognitive control VLPFC and affective modulating OFC-temporo-limbic regions. Moreover, given that the PFC (OFC, DLPFC, IFC, vmPFC, dmPFC) (found to be functional abnormal during error processing, sustained attention and processing of fearful and

neutral faces), ACC (found to be functional abnormal during sustained attention, error and fear processing), striatum (found to be functional abnormal during sustained attention and processing of fearful and neutral faces) and anterior cerebellum (found to be functional abnormal during sustained attention and processing of neutral faces) develop relatively late structurally and functionally by late adolescence (Shaw et al., 2008; Ostby et al., 2009; Giedd et al., 2010; Rubia, 2013), they may be more susceptible to impairment following childhood adversities. Hence, abnormalities of these late-developing DLPFC/IFC/dmPFC-cingulo/SMA-striatal-cerebellar and vmPFC-temporo-limbic regions that are known to mediate late-developing cognitive and affective functions, respectively, suggest an environmentally triggered disturbance in the normal development of these networks that may underlie the cognitive and emotional problems that develop as a consequence of childhood abuse.

10.3. Strengths and Limitations of the Study

10.3.1. Strengths

This PhD project contributes to the existing neurobiological research on childhood maltreatment by conducting the first meta-analysis of published whole-brain VBM studies of structural abnormalities in childhood maltreatment to elucidate the most robust volumetric GM abnormalities relative to non-maltreated controls (Chapter 6). Next, it investigated the functional abnormalities associated with severe childhood (physical) abuse in three reasonably sized groups of age- and gender-matched young people ($N \geq 20$) using whole-brain fMRI (Chapters 7-9) and adds on to the current fMRI research on childhood maltreatment by 1) including a psychiatric control group that is matched on psychiatric comorbidities with the participants who

had experienced abuse to separate the confounding effects of comorbid psychiatric disorders, 2) controlling for psychoactive medication and drug abuse by recruiting medication-naïve and drug-free young people, and 3) using rigorous assessment of childhood abuse by conducting the CECA interviews additionally to substantiate the information from the CTQ and corroborating the abuse experience with social service records.

It is crucial to include a third group of psychiatric controls as currently most studies did not control for psychiatric comorbidities making it unclear whether the neurobiological abnormalities observed can be attributed to childhood maltreatment, or the associated psychiatric conditions, or a combination of both. It is also imperative to control for drug abuse as it has been shown to affect brain structure and function (Goldstein and Volkow, 2011) as well as to control for psychoactive medications as they are also known to affect brain structure and function (Murphy, 2010; Nakao et al., 2011), so that the reported brain abnormalities associated with childhood maltreatment are not confounded by long-term medication and/or drug effects.

Furthermore, several studies have included participants with various forms of childhood maltreatment such as sexual, physical and emotional abuse, emotional and physical neglect, verbal abuse, early deprivation and witnessing domestic violence (please see Tables 3 & 4). Given that different types of childhood maltreatment differ in their clinical presentation, it is conceivable that different types of maltreatment may also have different neurobiological, psychiatric and behavioural effects on the individual. For instance, childhood sexual abuse has different effects on brain

structure (Heim et al., 2013) and has different psychiatric and behavioural consequences (Ackerman et al., 1998). It is thus important to examine the effects of various types of childhood maltreatment separately. This PhD project attempted to do this by examining the neural correlates of (severe) childhood physical abuse. However, it may be unrealistic to separate physical abuse from typically co-occurring emotional abuse and neglect (Edwards et al., 2003), as it is unlikely for the individual with a history of childhood maltreatment to experience *severe* physical abuse without experiencing at least moderate levels of emotional abuse and neglect concurrently; on the other hand, physical abuse does not always co-occur with sexual abuse. Moreover, using child protective services case records abstraction (physical, sexual, emotional abuse and neglect), latent class analysis revealed four distinctive profiles of childhood maltreatment experiences in which physical abuse was clustered with 1) neglect, 2) emotional abuse, 3) both neglect and emotional abuse and 4) neglect, emotional abuse and sexual abuse (Trickett et al., 2011). Thus, this project helps to extricate the influence of childhood sexual abuse on the findings by recruiting participants with a documented history of childhood physical abuse but without reported sexual abuse.

10.3.2. Limitations

Nonetheless, it is acknowledged that this is a mixed sample of young people that had been exposed to considerable levels of childhood emotional abuse and neglect in addition to severe physical abuse and hence the need to discuss more broadly about childhood maltreatment in general as a predictor of the observed patterns of abnormal neural activation. Additionally, it is unclear to what extent pubertal development, malnutrition and prenatal drug exposure may have influenced

the findings. Finally, the cross-sectional design of the project limits the ability to make causal inferences between childhood maltreatment and the structural and functional abnormalities reported.

10.4. Contributions to Knowledge

This PhD project furthers our understanding on the association between childhood maltreatment and structural brain deficits and neurofunctional abnormalities in error processing, sustained attention and emotion processing; controlling for the confounding effects of psychiatric comorbidities, medication and drug abuse. The inclusion of a third group of psychiatric controls enabled us to examine the specificity of association with childhood maltreatment. Hence, the novelty contributions of this project include the findings of abuse-specific abnormally enhanced activation in classical dorsomedial frontal error processing regions particularly the SMA, as well as in vmPFC and ACC regions of fear processing, presumably reflecting hypervigilance to errors and fear signalling potential threat and danger in the environment. There was also an abuse-related functional impairment in the dorsal and ventral fronto-striato-thalamo-cerebellar sustained attention regions during the most challenging attention condition only and an abuse-specific progressively deteriorating activation with increasing attention loads/delays.

Furthermore, these findings suggest that young people who had experienced childhood abuse may not be globally impaired in either the cognitive or emotion domain; but rather, they showed a heightened sensitivity to signs or cues (e.g. errors, fearful faces) that may signal potential danger and threat, likely due to the precarious

abusive home environment they grew up in. Although the enhanced fear and error processing may possibly confer short-term functional benefits by allowing the individual to rapidly detect threat and hence avoid potential danger/abuse in an abusive context, they may lead to maladaptive behaviours in more normative situations; with aberrant processing of errors and threat cues increasing the individual's risk for anxiety and other emotional and conduct problems later. This is particularly evident in the abnormally enhanced activation in fronto-striato-temporo- limbic and cerebellar regions to neutral faces and the negative perception bias of neutral faces, which is likely to be maladaptive and is similar to that observed in MDD and anxiety disorders (Cooney et al., 2006; Maniglio et al., 2014). These neurofunctional abnormalities may possibly be one process through which environmental adversities lead to the development of psychopathology and maladaptive behaviours in the longer-term.

10.4.1. Future Directions

Future studies could build on this project and include a fourth group of healthy participants exposed to childhood maltreatment but who do not have any psychiatric disorders, which would allow us to examine the neurobiological basis of resilience to childhood maltreatment. The inclusion of this group of resilient young people would have been a stronger control group to determine abuse-specific deficits. In fact, the original PhD project did propose to examine this unique group of resilient healthy young people who had experienced severe childhood physical abuse but unfortunately it was too difficult to recruit enough of them within the short time-frame of the project. The high level of abuse severity that this project is interested in might also have hindered the recruitment of these *highly* resilient young people

within the duration of the project. In contrast to the vast number of studies on protective psychological factors, studies on the neurobiological mechanisms involved in resilience to early adversity is relatively limited (van der Werff et al., 2013). Future longitudinal studies with increased sample sizes are also needed to identify causal associations between childhood maltreatment and abnormalities in brain structure and function, to better understand the role of impairments in mediating future outcomes as well as to identify mechanisms underlying resilience.

Furthermore, given that different brain regions develop and mature at different rates (Gogtay et al., 2004), it is conceivable that traumatic, such as childhood maltreatment, may have different detrimental effects on the various brain regions depending on the age of exposure to the trauma. Hence, it would be valuable to compare the effects of the same form of childhood maltreatment in individuals who had been victimised at different ages or at windows of vulnerability. Future studies may also like to compare larger samples of young people of different pubertal status to identify specific effects of puberty on the observed patterns of atypical neural responses. Other factors, such as genetic contributions to risky abusive family environments that were not assessed in the present project, may contribute to both the neural patterns of activation and abusive family experiences.

Last, given evidence of gender differences in structural and functional brain maturation between childhood and adolescence (De Bellis et al., 2001; Brenhouse et al., 2011; Rubia 2013), childhood maltreatment may also have differential neurobiological effects on boys and girls at different developmental stages. The present study was underpowered to examine gender and age differences and their

interaction effects; hence, future studies should explore potential gender differences and/or age by gender interaction differences on brain functions as a consequence of childhood maltreatment. Furthermore, studies that have examined gender differences in the effects of childhood maltreatment on behaviour and psychological outcomes have found mixed findings. For instance, although childhood maltreatment has negative health consequences for both men and women, it was found to be more detrimental for women as only females who had experienced childhood maltreatment were at increased risk for MDD, suicidal or drug abuse (MacMillan et al., 2001; Thompson et al., 2004). However, some studies have also suggested that females may be more resilient to the effects of stress than males (McGloin and Widom, 2001; Dumont et al., 2007). Interestingly, a recent study by Samplin et al (2013) found that females were more resilient to the neurobiological effects of childhood maltreatment but not to the psychiatric symptoms associated with childhood maltreatment. Hence, future studies are needed to elucidate the mechanisms involved in resilience at both the neurobiological and psychological levels (Samplin et al., 2013).

10.4.2. Implications for Clinical Interventions

Clinically, understanding how individuals who had experienced childhood abuse differ from healthy individuals may lead to more targeted treatment strategies. For instance, the young people with a history of abuse showed normal brain activation and performance to all emotions except for fearful and neutral emotions. They do not have a global deficit in emotion processing in general but the prolonged hyper-reactivity of fear processing in the absence of any real threat may ultimately manifest as clinical symptoms, for example in the form of anxiety and reactive aggression. Similarly, the abnormally enhanced activation to neutral faces and the

negative perception bias of neutral faces may also lead to atypical social information processing which could potentially lead to the aggressive behaviour observed in physically maltreated young people (Shields et al., 1998).

Therefore, targeted interventions could be developed for these young people to build normal internal representations of self and especially of others (e.g. schemas or internal working models) and encourage a focus on more normative interpretation of social stimuli to avoid the rapid identification of fearful expressions and ambiguous neutral encounters as threatening. Interventions including trauma-focused cognitive-behavioural therapy (CBT) (Cohen et al., 2000) that focuses on helping the individual who has experienced childhood abuse to examine and assign appropriate emotional meaning to the traumatic experience as well as to normal events experienced in daily life may help to extinguish and decondition the exaggerated fear responses learned during childhood.

Childhood maltreatment is an interpersonal trauma which may disrupt the normal process in which a child develops models of relationships based on early interactions with parents/caregivers. Given that the (abusive) parent/caregiver, who is tasked with creating a safe environment for the growing child, is often the source of stress for the child, young people who had experienced abuse are more likely to see others as untrustworthy and unpredictable (Dodge et al., 1990), and may therefore tend to misattribute other's neutral expressions as negative or even malevolent. Thus, interventions should focus on resolving trauma-related attachment disruptions, correcting distorted perceptions of others and developing the competencies necessary to form and maintain supportive trusting interpersonal relationships which may

provide a potential source of safety and security for the vulnerable young people with a history of abuse. Neurobiological evidence further supports the importance of having a reliable adult caregiver to help scaffold the vulnerable child's ability to regulate stress (Dozier et al., 2006, 2008). Hence, interventions aimed at strengthening social support systems for these individuals may be useful in coping with and healing from the childhood trauma.

Similarly, individuals who had experienced childhood abuse do not have a global cognitive deficit but have a hyperactive error processing network which may help to rapidly detect mistakes and hence avoid potential punishments in an abusive context. The constant hyper-reactivity of error processing in the absence of any punishment may lead to symptoms of anxiety, depression and self-blame. Moreover, harsh and critical reprimand over a mistake from authority figures, such as teachers and employers, may also put additional unwarranted stress on vulnerable young people with a history of childhood abuse (who already have a hypersensitive error monitoring system) and exacerbate, albeit unintentionally, the underlying psychopathology of anxiety and depression associated with early adversities. Interventions may thus include helping these young people who had experienced childhood abuse to “unlearn” the association between error and harsh punitive punishment that was erroneously learned during childhood.

The deficits in sustained attention networks only manifested during the most challenging attention condition; hence, the young people who had experienced childhood abuse seemed to have less pervasive neurofunctional attention deficits than people with ASD and ADHD (Christakou et al., 2013; Murphy et al., 2014),

who demonstrated attentional impairment in all attention/delay conditions in the same task. Attention training to improve sustained attention may be helpful for these individuals exposed to abuse. Alternatively, since children exposed to trauma are differentiated from ADHD children without trauma on the basis of their dissociative symptoms (Reyes-Perez et al., 2005), inattention observed in the young people who had experienced childhood abuse may be related to dissociation and affective dysregulation (Andrea et al., 2012), which could possibly be improved following interventions on emotion-regulation and self-regulation.

Ultimately, it is hoped that a better understanding of the neurobiological underpinnings of childhood maltreatment will lead to the development of treatments aimed to normalize these experience-induced neurobiological abnormalities.

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